Chronic, unexplained pain

T.J. Snijders

Cover design Tom Snijders; original figure (illustration of the pain pathway): René Descartes, Traite de l'homme, 1664.
Layout Renate Siebes, Proefschrift.nu
Printed by Ridderprint, Ridderkerk
ISBN 978-90-393-5775-0

Chronic, unexplained pain

Chronische, onverklaarde pijn

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht op gezag van de rector magnificus,
prof.dr. G.J. van der Zwaan, ingevolge het besluit van het
college voor promoties in het openbaar te verdedigen
op dinsdag 12 juni 2012 des ochtends te 10.30 uur

door

Thomas Jan Snijders

geboren op 2 juli 1978
te Utrecht

Promotoren: Prof.dr. J. van Gijn
Prof.dr. N.F. Ramsey

Co-promotor: Dr. A.J.M. van Wijck

The studies in this thesis were financially supported by the Catharijnestichting (chapters 4, 5, 8), the Stichting Janivo (chapters 4, 5, 8), the Stichting K.F. Hein Fonds (chapters 4, 5, 7, 8), The Fonds Psychische Gezondheid (chapters 7, 8), the Jan Dekkerstichting en dr. Ludgardine Bouwmanstichting (chapter 8) and the Sara Lee Foundation (chapters 4, 5, 8). The authors performed all aspects of these studies (design, data acquisition, analysis, writing of papers, decision to submit) independently of these organizations.

For the publication of this thesis, financial support from the J.E. Jurriaanse Stichting is gratefully acknowledged.

Contents

1

Introduction

Partially based on Snijders TJ, Ramsey NF, Van Gijn J.
Ned Tijdschr Geneesd 2007;151:461-5

CASE VIGNETTE

Mrs. A.,* a 60-year old widow, visits the Neurology outpatient clinic because of severe pain in the low back, legs, neck and shoulders. Her general practitioner referred her at her own request to see if a neurological cause for her symptoms could be found, and whether other treatment options might exist.

The patient reports to have had pain in neck, back, shoulders and – to varying degree – in the hips and legs for as long as she remembers. An increase of pain occurred in the last few months, without any obvious reason. The pain is constantly present; she describes it as a 'terrible, unbearable muscle' pain. All movements and even mild pressure on her muscles lead to an increase in the pain she experiences. Although the back pain sometimes spreads to the hips during exacerbations of pain, she does not notice any radiation to the legs. Her muscles feel less strong but she reports no weakness in specific muscles.

Her medical history includes surgery of the lumbar spine for a herniated intervertebral disc, twenty years before. At that time, she suffered from back pain with some radiation into the right leg, but even then her pain was more widespread, with involvement of shoulders and neck. For a long time she feels that her pain is the symptom of an underlying and undiscovered disease. However, consults with a rheumatologist, an orthopedic surgeon and another neurologist in the last two years did not lead to a specific diagnosis and she was told repeatedly that 'nothing was wrong' and that she needed to learn to 'live with the pain'. Since movements such as walking, cycling and sitting in the same position for a long time led to more pain, she feels that movements 'damage her muscles' and she increasingly avoids physical activity. She reports often feeling sad and isolated, a feeling that has grown since her husband died, three years before. Her son lives abroad and although she has many friends, she sees them less and less because she does not want to travel – as this leads to more pain – and because her friends 'do not understand her when she talks about her pain'.

The patient has used paracetamol, ibuprofen and tramadol infrequently, with varying effect. Her physiotherapist massages her back and neck every week, which offers relief for a few hours each time. She was offered psychological counseling by her family physician, but refused this since she 'has pain, not a mental problem'.

On physical and neurological examination, no abnormalities of joints or spine are noted. Also, no muscle weakness, reflex abnormalities or sensory deficits are found. Straight leg raising tests are negative. During the examination, the patient reports pain during most movements, passive as well as active.

* Certain personal details in this case have been changed in the interest of the patient's privacy.

The patient in this case vignette suffers from long-lasting pain for which physicians did not find a conventional medical cause: chronic, unexplained pain (CUP). At first glance, she has a health problem that consists solely of pain. On second look, several problems other than the pain itself are important. Apart from spontaneous pain of back and limbs, she also experiences an abnormally strong sensation when she moves, or in response to external stimuli. She is afraid that the pain is a signal of her body telling her that she is damaging her muscles; consequently, she increasingly refrains from physical activity. She experiences social isolation. Over the years, she visited many healthcare professionals in search of pain relief, to little avail. Also, this quest through the healthcare system supplied her neither with a satisfactory explanation for her symptoms, nor with the feeling of reassurance that she does not have a life-threatening or progressive medical condition.

This thesis focuses on the many aspects of CUP that are featured in the case vignette: from the pathophysiology of abnormal pain sensation, via pain sensitivity and clinical symptoms, to the overall clinical profile – including psychological aspects – and outcome of patients with CUP. By studying these many facets, sometimes in an isolated, controlled fashion, and sometimes simultaneously, we intend to increase the body of knowledge on the complex interplay between neurobiological, psychological and social factors in CUP.

In this chapter, we introduce basic concepts concerning current clinical practice, definition, epidemiology and pathophysiology of CUP before further outlining the contents of this thesis.

CHRONIC, UNEXPLAINED PAIN: CURRENT CLINICAL PRACTICE

Most general practitioners and many medical specialists are consulted by many patients like Mrs. A. In this paragraph we summarize the current clinical practice concerning diagnosis and treatment of patients with CUP and we identify areas where knowledge is limited.

Diagnosing CUP is essentially based on two items: (1) the patient's report of pain; and (2) the exclusion of an underlying medical cause. Rather than just describing symptoms as CUP, many clinicians prefer to use a diagnostic label such as fibromyalgia or irritable bowel syndrome. These 'functional pain syndromes' (FPS) are symptom-based diagnostic categories; the most common ones are listed in table 1.1. The pathophysiological validity and clinical utility of these diagnostic labels is controversial.[1]

Because the diagnosis of CUP is made by excluding an underlying medical cause, patients and physicians may experience continuing uncertainty, because they fear that a medical cause has been overlooked. Follow-up studies on medically unexplained symptoms (MUS) suggest that the proportion of missed diagnoses is small,[2,3] but this was not studied specifically in CUP patients. None of the available clinical characteristics has a strong positive predictive value

Table 1.1 Some of the most common functional pain syndromes (listed in alphabetical order)

Fibromyalgia
Irritable bowel syndrome
Non-specific (low) back pain
Painful bladder syndrome/Interstitial cystitis
Temporomandibular joint disorder
Tension-type headache
Vulvodynia
Whiplash-associated disorder

for the diagnosis of CUP. Certain clinical features have been associated with CUP and other unexplained symptoms, but empirical evidence to support the diagnostic utility of these features is largely lacking. For example, long-used positive signs such as the 'belle indifference' – a patient's apparent lack of concern towards his or her symptoms – turns out to be unreliable in distinguishing neurologically explained muscle weakness from unexplained weakness (motor conversion disorder).[4] Also, conditions like depression and anxiety disorders are often associated with CUP,[5] but their positive predictive value for a diagnosis of 'unexplained' pain is unclear; however, recognition of co-morbid depression or anxiety disorder is still important because of their possible role in maintenance of symptoms.[6]

Once a clinician diagnoses CUP, therapeutic management starts as soon as this conclusion is communicated to the patient. Recognizing that the patient does experience pain, even in absence of an identifiable cause, as well as the use of the right terminology,[7] prevents the possibility that the patient feels that he or she is not taken seriously or that the clinician thinks that the pain is 'not real' or 'imagined'.

Since unexplained pain and other MUS are common and most symptoms are self-limiting in nature, most guidelines and reviews suggest a stepped-care approach (box 1.1). Most patients will benefit from step 1a, which consists of recognition of the symptoms, communicating that no threatening medical condition was found, short-lasting symptomatic (analgesic) treatment and psychoeducation on self-management of symptoms.[8] For those who do not sufficiently benefit after this first step, several options are available. These treatments have mostly been evaluated for the separate FPS, especially pharmacological treatment for highly prevalent conditions such as fibromyalgia. Centrally acting medication such as (tricyclic) antidepressants, cognitive-behavioral therapy aimed at illness-related cognitions and active types of physical (exercise, physiotherapy) have proven successful in several FPS.[8]

Box 1.1 Stepped care (adapted from Henningsen et al.)[8]

Step 1a: uncomplicated FSS
- Reassurance with positive explanation of FSS; do not only convey negative test results
- Symptomatic measures like pain relief
- Advise graded activation or exercise rather than rest

Step 1b: complicated FSS
- Measures as in step 1a for current main symptom
- Consider antidepressant treatment
- Advise on dysfunctional attributions and illness behavior and encourage reframing of symptoms within biopsychosocial framework (i.e., incorporate both the patients' beliefs about the organic nature of their symptoms and how these can be affected by a range of psychological and contextual factors)
- If appropriate: appointments at regular intervals rather than patient-initiated

Step 2: if either step 1a or step 1b prove to be insufficient
- Prepare referral to psychotherapist or mental-health specialist with reappointment
- Ensure that traumatic stressors and maintaining context factors, such as litigation, are assessed
- Continue with appointments at regular intervals rather than patient-initiated
- Liaise with psychotherapist or mental-health specialist on further treatment planning and difficulties

Step 3: If step 2 proves insufficient and if available
- Multidisciplinary treatment including symptomatic measures, activating physiotherapy, and psychotherapy

However, many patients still experience insufficient relief from the available measures. In spite of progress in etiological and therapeutic research on CUP, current clinical management of CUP is still impeded by the limited knowledge on causative, perpetuating and exacerbating factors in CUP.

DEFINITION

CUP may be defined as pain for which no conventional medical cause is found and that lasts for more than 3-6 months. This definition is descriptive in nature; it does not imply any underlying mechanism or specific clinical profile. Further definition follows from the three elements of CUP:

1. **Pain** is defined by the International Association of Pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'.[9] The central concept in this definition is an individual's experience – not the noxious stimulus or the associated tissue damage. The relationship between noxious stimuli, pain perception, suffering and pain behavior is often depicted as a circle model, which is based on work by Loeser and Black (figure 1.1).[10] Nociception, the neural process of encoding noxious stimuli, lies at the heart of this model. The

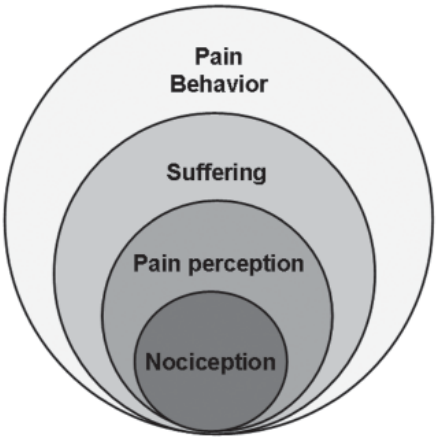

Figure 1.1 The circle model of pain, which is based on work by Loeser and Black.[10]

nociceptive signal is transported from the nociceptor, via modality-specific (A-delta and C-) peripheral sensory nerve fibers, to the dorsal horn of the spinal cord through the spinothalamic tract before reaching the brain. Pain perception is the registration of pain at the cerebral level. This basic signal is then integrated with competing and modulatory cerebral processes to result in pain suffering, which may be defined as the response of the intact organism to perceived nociceptive input. Finally, pain behavior consists of those behaviors that are externally observable, such as lying down or grimacing.[10] In acute pain, such as the pain that directly follows a traumatic injury, these different pain dimensions are usually organized in a more or less linear and hierarchical manner; in chronic pain, they often are not.

2. **Chronic** – In contemporary pain research, chronic pain is usually not defined by its duration, but rather as pain that lasts after the source of nociception has disappeared. In this definition, chronicity of pain is mainly defined by the occurrence of a physiological process wherein a pain signal is produced independent of a noxious stimulus. This definition overlaps with the definition of CUP. In this sense, CUP can be considered as an extreme within the spectrum of chronic pain: chronic pain is characterized by an uncoupling of pain from its original nociceptive source, CUP by the absence of such a nociceptive source. Further characteristics of acute *versus* chronic pain are listed in table 1.2.
3. **Unexplained** – The 'unexplained' nature of a patient's pain refers to the absence of a conventional medical cause. By definition, this label can only

Table 1.2 Characteristics of acute and chronic pain

Acute pain	Chronic pain
Known source of nociception	No known source of nociception, or an uncoupling of nociceptive source and pain experience
Symptom of an underlying disease	'Disease in its own right'
Alarm function	Dysfunctional signal
Duration of less than 3-6 months	Duration of more than 3-6 months
Predictable	Psychosocial consequences
Self-limiting	

be applied once known medical (or: 'organic') causes have sufficiently been ruled out. 'Unexplained' is different from 'unexplainable', since the latter term implies that it is impossible to gain further knowledge, now or in the future. Unexplained pain is the key feature of the psychiatric diagnosis of 'somatoform pain disorder'; in the criteria for this diagnosis, the role of psychological factors in the onset, severity, exacerbation or maintenance of pain is emphasized. Several authors have criticized this criterion – and the diagnosis 'somatoform pain disorder' in general – since it is difficult to prove (rather than assume) the role of psychological factors in clinical practice.[11] Also, the role of psychological factors is important in most – if not all – types of chronic pain and not just CUP.[12]

Related to the definition of CUP and other MUS is the concept of somatization: a tendency to experience and communicate somatic distress and symptoms unaccounted for by pathological findings, to attribute them to physical illness, and to seek medical help for them.[13] This concept is related to CUP and other MUS in that unexplained symptoms form a characteristic feature, but somatization is defined as a type of behavior that a person displays rather than as a symptom that the patient suffers from.

Due to the many concepts and corresponding theories that exist about MUS and CUP, clinicians use many different terms to address MUS and CUP, such as functional, idiopathic, psychogenic, hysterical and non-organic. Previous research has shown that the term ´functional´ is best accepted by patients.[7] In this thesis, we use the term 'unexplained'; this term is neutral in the sense that it does not imply any underlying mechanism or cause. We use this term with the explicit intention to have it replaced in the future by a term that specifically addresses the underlying mechanism(s) of CUP.

MEDICALLY UNEXPLAINED SYMPTOMS AND FUNCTIONAL PAIN SYNDROMES

Many people report symptoms for which no medical cause is found. Medically unexplained symptoms (MUS) may consist of a variety of complaints such as pain, nausea, dizziness, muscle weakness and abdominal discomfort. Pain is one of the most common MUS. Since long, clinicians and researchers have used syndrome-based diagnostic labels. Many of these functional somatic syndromes' have pain as a core feature; they are collectively referred to as 'functional pain syndromes' (FPS) (table 1.1).[14] Most of the unexplained syndromes for which pain is not a core feature, such as chronic fatigue syndrome, still are associated with pain.[15]

For an equally long time, the validity of these syndromes as diagnostic labels is subject of debate. The syndromes are, more or less by definition, characterized by a lack of objective and reproducible abnormalities such as laboratory or radiological tests. Each have their own set of criteria, consisting of a list of symptoms, based on the patient's report, and often findings on physical examination such as the finding of tender points in fibromyalgia.[16] Several lines of evidence support the idea that the FPS are part of a single clinical spectrum rather than distinct clinical and pathophysiological entities.[1] Many or most patients with one FPS meet the criteria for one or more other FPS.[17,18] Major overlap in psychological characteristics and co-morbidity between syndromes has been found, such as high rates of anxiety and depression.[19,20] Many FPS are associated with high rates of pain catastrophizing, which is defined as an exaggerated negative "mental set" brought to bear during actual or anticipated pain experience.[12,21] On the pathophysiological level, studies in several FPS have demonstrated hypersensitivity to painful stimuli,[22-24] and abnormalities in sensory processing in the central nervous system (CNS).[25-27]

Only the discovery of a defined cause, e.g. a genetic abnormality or infectious agent that is either common to the different FPS or different for each FPS, may unequivocally answer the question of whether FPS are distinct entities or not. The commonly accepted multifactorial background of these syndromes makes the future discovery of such an all-explanatory cause unlikely.[28] On the basis of the currently available evidence, we will consider all FPS as part of a single clinical spectrum throughout this thesis. Consequently, when we use the term 'chronic, unexplained pain', this includes all FPS as well as other patients with CUP (in whom no 'specific' FPS has been diagnosed).

PREVALENCE AND DIAGNOSTIC CHALLENGES

Specific data on the prevalence of CUP are scarce, since most previous studies focus either on the heterogeneous group of patients with any MUS, or on chronic pain in general (irrespective of whether the cause is known). A further difficulty in estimating the prevalence of CUP

follows from the uncertainty that is inherent to labeling symptoms as 'unexplained', because of the possibility that an actual medical cause was not identified. This uncertainty does not only hinder research on CUP, but may also complicate the counseling of patients on their symptoms.

Chronic pain is a major health problem because of its high prevalence, its great impact on daily living, and the large proportion of unsatisfactory results with available treatment. In a recent population-based study with over 46,000 participants from 15 European countries and Israel, 19% reported chronic pain.[29] The great impact of chronic on daily life was illustrated by the fact that 61% were less able or unable to work outside the house. In this study, the cause of symptoms was based on self-report, which makes it difficult to obtain a good estimate of the proportion with CUP; 12% of all patients did not know the cause of their pain.[29]

Medically unexplained symptoms are very common. In the specialist population, a substantial number of patients present with MUS; a study in seven medical specialties found that 52% of all new outpatients present with MUS, with rates differing per specialty from 37% to 66%.[30] In another study in a neurological outpatient clinic, 30% of new patients presented with MUS.[31] These studies did not specify what proportion of patients presented with pain. Only one study reports the proportion of patients with pain: among 1,144 neurology outpatients with unexplained symptoms, 26% presented with headache and 5.5% with other types of pain.[4]

As mentioned previously, studies that focus on the prevalence of (chronic) unexplained pain are scarce. General population studies report a wide range of prevalence estimates, from 2 to 40%.[32] The estimates depend strongly on the definition used. For example, the one-month prevalence of non-specific low back pain (regardless of exact duration, severity or cause) is almost 50%,[33] but the prevalence of chronic severe unexplained pain, defined by strict symptom-based criteria, was found to be only 0.8%.[34] Studies on the prevalence of the separate FPS generally report high rates, with an estimated point prevalence for fibromyalgia of 1-2% and for irritable bowel syndrome of more than 10%.[20,35,36]

A few studies focus on the question whether an initial diagnosis of 'unexplained' symptoms is reliable, or whether it is common that physicians find a (previously 'missed') medical cause for the pain at follow-up. Older studies report a rate of misdiagnosis of more than 30%, but this rate is much lower in more recent studies.[37] Although previous studies included patients with unexplained pain, there are no publications that focus specifically on misdiagnosis in CUP.

In summary, CUP and other MUS are common in the general population, although the exact prevalence is unknown – and depends on the definition used. The uncertainty of labeling symptoms as 'unexplained' is a problem both for clinicians and researchers in the field of CUP.

EPIDEMIOLOGY: DETERMINANTS OF CHRONIC, UNEXPLAINED PAIN

Certain clinical factors are associated with CUP and chronic pain in general, as reviewed by Smith et al.[38] Sociodemographic factors include female gender, older age, social class, cultural background, lifestyle, employment status and possibly occupational factors. [38-40] The psychological factors that are most consistently associated with CUP are anxiety and depression, dysfunctional coping styles, pain catastrophizing and a tendency for somatization.[12,19,38,41,42] Since many previous studies were cross-sectional in design, it is unclear whether the identified factors are cause or consequence of CUP.

Irrespective of their etiological position, some of these factors have proven prognostic value, mostly in predicting whether acute pain symptoms will transform into chronic pain. Depressed mood, somatization and distress have been associated with prognosis (including risk of chronicity) in low back pain.[21] After acute flexion-extension (whiplash) injury, long-term pain and disability were associated with baseline older age, high rates of psychological (post-traumatic) distress, severe initial pain and some physical characteristics of pain sensitivity.[43]

Once pain has become chronic, there is little empirical evidence to predict which patients will remain in pain and which patients will improve. In a population-based cohort of patients with unexplained pain of any duration, female gender and depression at baseline were associated with persistence of pain.[6] In a group of patients with musculoskeletal pain, baseline anxiety, depression, pain intensity, physical condition and coping style were predictive of a positive effect of a multidisciplinary rehabilitation program.[44] Involvement in legal procedures is associated with poor outcome in chronic pain.[45]

Further knowledge on prognostic and predictive factors in CUP will be of obvious use for clinical practice. In addition, identification of such factors may provide further insight into the underlying causes of CUP.

ETIOLOGY: BIOPSYCHOSOCIAL MODEL

CUP, and chronic pain in general, is heterogeneous in its clinical presentation. By definition, no conventional medical cause can be identified in CUP; in other (explained) forms of chronic pain, an uncoupling of pain from its original nociceptive source is also common.[9] Despite this heterogeneity of symptoms and the absence of a straightforward cause, research into chronic pain throughout the last decades has led to an etiological framework which is based on the biopsychosocial model (figure 1.2). A key feature of this model is the notion that the study and management of a patient's disease should not only focus on identification and treatment of neurobiological factors, but should also take psychological and social factors into account.[46] The

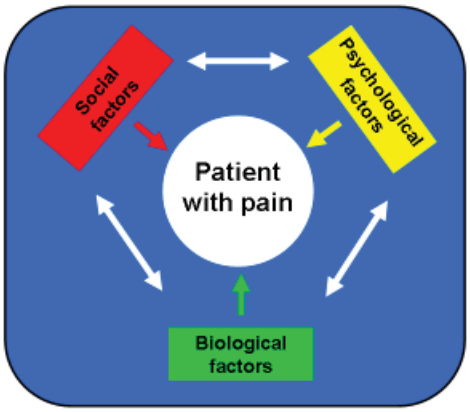

Figure 1.2 The biopsychosocial model of pain.

importance of psychosocial factors in CUP is clear from the epidemiological evidence (discussed in the previous paragraph) for the strong association between chronic (unexplained) pain and factors such as depression, coping style and social class. The case of Mrs. A. also illustrates how chronic pain is often accompanied by dysfunctional cognitions about pain (her persistent belief that an underlying cause for pain was missed by physicians; associating movement with muscle damage), depressed mood, and social isolation. The biopsychosocial viewpoint is further supported by the fact that cognitive-behavioral therapy is effective – though not universally – in the treatment of CUP.[47]

The biopsychosocial model has proven very useful in preclinical and clinical research on chronic pain. The model is not specific for CUP, but may also be applied to chronic pain of explained origin. As an example, the pain intensity that individual patients with osteoarthritis and rheumatoid arthritis experience is not just related to physical and biochemical markers of disease severity, but also to the degree of pain catastrophizing.[12]

The neurobiological factors in chronic (explained) pain include the underlying disease that formed the original source of pain, such as rheumatoid arthritis or nerve root compression by a herniated intervertebral disc. However, chronic pain usually exceeds the consequences of the original disease and in CUP this factor cannot be identified at all. One of the aspects of the biopsychosocial model that requires further study is the neurobiological mechanism by which several factors are linked to pain. Stated otherwise: via which pathophysiological route do biological, psychological and social factors lead to the experience of pain in an individual patient? In the following paragraphs, we discuss the role of (a) abnormalities in intrinsic pain sensitivity; and (b) dysfunctional cerebral pain processing as mechanistic factors in the pathophysiology of CUP.

PATHOPHYSIOLOGY: PAIN SENSITIVITY

An individual's pain sensitivity is usually studied by measuring pain thresholds: the intensity that a certain stimulus needs to have before a person experiences it as painful. An alternative method is measuring a person's subjective experience of an applied painful stimulus by means of a pain rating scale such as a visual analogue scale (VAS). Pain thresholds and the subjective experience of painful stimuli are dependent on the signaling system that transports the nociceptive stimulus to the brain, where it leads to the conscious perception of the stimulus and eventually to the patient's response. Also, pain thresholds and pain ratings are dependent on the patient's experience and report, which may be influenced by emotions and cognitions concerning the stimulus and pain in general. Because of this dependence on both the basic nociceptive processing and the higher-order cerebral processes, pain sensitivity may be seen as an intermediate step between the patient's clinical pain symptoms and the underlying pathophysiological mechanism.[48] Although the experience of pain is a subjective phenomenon, it can be quantified by measuring a patient´s standardized responses to a stimulus of a set strength and modality. Such psychophysical tests are often used in pain research and are collectively known as ´quantitative sensory testing´ (QST).[49] QST is a term that may encompass any number of different tests, including painful and non-painful stimuli of different modalities, e.g. mechanical, thermal or vibration stimuli.[50]

Pain sensitivity is dependent on many factors and may be influenced by many external and internal competing stimuli. The amount of attention that a person pays to a painful stimulus is an important determinant of the subsequent pain experience: attention to pain usually increases pain ratings, whereas distraction diminishes the pain experience.[51] In chronic pain, the influence of attention on pain experience differs from healthy subjects.[52] Chronic pain patients may have a problem allocating attention to competing pain stimuli.[53]

A central concept in many clinical pain states is sensitization, which is defined as increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs.[54] Sensitization has an evolutionary role as an adaptive process to increase detection of noxious stimuli in the context of danger, but this function of sensitization is lost in the context of chronic pain. Sensitization in chronic pain may occur at the level of the peripheral receptor (nociceptor), but it can also have its origin in the CNS (central sensitization), at the level of the dorsal horn.[55] Neuronal systems in the dorsal horn serve as a 'gate' that controls the degree by which incoming signals are transported to the brain; this gate is under influence, among others, of top-down-influences from the brain, which forms another potential source of sensitization.[56] An increasing body of evidence supports a major role of central sensitization, particularly involving cerebral mechanisms,[27] in a variety of chronic pain conditions, including fibromyalgia and other FPS.[57]

In CUP, many studies have demonstrated increased sensitivity to painful stimuli. A study that compared patients with localized CUP (temporomandibular joint dysfunction) and widespread CUP (fibromyalgia) found hypersensitivity to pain throughout the body in both patient groups.[22] In a study from the 1990s, fibromyalgia patients reported higher pain ratings than healthy subjects or patients with explained pain in response to the same painful stimulus, but they also reported higher unpleasantness ratings for a standardized auditory stimulus (loud noise).[24] This suggests that CUP patients are hypersensitive to a variety of sensory stimuli, a phenomenon that is often attributed to the interaction with attention alluded to above. An abnormally strong, automatic focus of attention towards (potentially) unpleasant bodily signals, especially pain, is termed 'generalized hypervigilance'.[58] Whether hypervigilance is truly generalized across modalities or specific to pain is subject of debate.[59,60] The generalized hypervigilance theory states that attentional bias (which must occur at the cerebral level) causes amplification of afferent signals, implying that afferent signals from all body regions are amplified. Few studies have investigated whether pain hypersensitivity in CUP is indeed spatially generalized.

In summary, hypersensitivity to pain is a common finding in CUP and may form an important intermediate step between clinical pain experience and underlying pain mechanisms. Many questions remain on the exact characteristics and the spatial extent of (attention-dependent) pain hypersensitivity as well as its relation to clinical characteristics of CUP. Recent research has given better insight into the neural underpinnings of pain hypersensitivy and generalized hypervigilance in CUP, as is discussed in the next paragraph.

PATHOPHYSIOLOGY: CEREBRAL PAIN PROCESSING

In the last 20 years, knowledge on cerebral processing of pain in healthy persons and in different disease states has greatly increased. This is mostly because of the advances in functional neuroimaging techniques such as positron emission tomography (PET), magneto-encephalography (MEG), and – most prominently – functional MRI (fMRI). fMRI makes use of the natural magnetic contrast between oxygenated and deoxygenated hemoglobin. When a brain region is active in response to a stimulus or in relation with a cognitive task, this region is supplied with an excess of oxygenated blood. With conventional clinical MRI scanners, this blood oxygenation level dependent (BOLD) effect is quantifiable and serves as an indirect, non-invasive measure of regional brain activity with high spatial resolution (but lower temporal resolution).[61]

The cerebral processing of noxious stimuli in healthy persons involves activity in a network of brain regions that is commonly referred to as the *pain matrix* (figure 1.3).[62] Activity in this

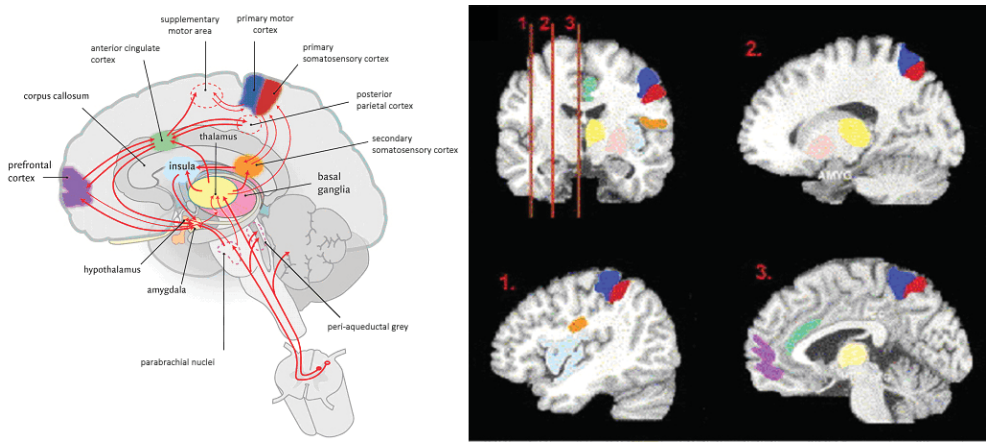

Figure 1.3 The *pain matrix*: brain regions commonly associated with the cerebral processing of pain. Figure adapted from Ned Tijdschr Geneeskd 2007;151:461-5. Printed with permission.

network is often subdivided in sensory-discriminative and emotional-evaluative aspects of pain processing, although these functions are both conceptually and topographically not strictly separable. Regions that most consistently show pain-related activity in functional neuroimaging studies include the primary and secondary somatosensory cortices, insular cortex, thalamus, anterior cingulate cortex and (dorsolateral) prefrontal cortex.[62] Recently, some authors question the specificity of the *pain matrix* regions for pain processing and suggest that this network serves as a salience detection system that is not limited to pain processing.[63,64]

Since long, it is known that cerebral pain processing is a two-way phenomenon: afferent (painful and non-painful) signals as well as cognitive processes may lead to the activation of feedback loops that project – via several brainstem regions – on the dorsal horn neurons (the 'gate' neurons in the gate-control theory). Essential in this descending pain modulatory system (DPMS) is the interplay between prefrontal cortex, brainstem regions and the limbic system, with an important role for anterior cingulate and insular cortex.[65] The anterior cingulate cortex is also a key region in several studies on modulation of pain processing according to different attentional states.[51,66]

The growing knowledge on cerebral pain processing stimulated further research into the central mechanisms involved in chronic pain. This line of research is of special interest for the study of CUP syndromes; the lack of any identifiable peripheral cause of CUP as well as the association of CUP with cognitive (e.g. attentional) and emotional phenomena both suggest that CNS mechanisms are pivotal in the pathophysiology of CUP. Early studies in fibromyalgia demonstrated that pain sensitivity was associated with stronger cerebral responses

to standardized stimuli in fibromyalgia patients than in controls, and that brain activity was most abnormal in those patients who exhibited a high degree of catastrophizing.[25,67] In irritable bowel syndrome, brain activity in relation to rectal distension differed between patients and controls.[68] Differences that were found between CUP patients and controls included activity in prefrontal cortex, insula and anterior cingulate cortex. More recent studies shed further light on differences between spontaneous (disease-related) and evoked (stimulus-related) pain in low back pain,[26] and the role of abnormalities in brain activity during rest.[69,70] Although several studies focus on the role of attention in cerebral pain processing,[51,71] we are not aware of any published studies on attention-related pain processing in CUP.

OUTLINE OF THIS THESIS

This thesis is divided into two parts. In Part I, we study epidemiological aspects of CUP. In part II, we zoom in on the pathophysiology of CUP with a focus on pain sensitivity and cerebral pain processing. Box 1.2 lists the research questions that we aim to answer in this thesis.

Box 1.2 Research questions

Part I: Epidemiology

1. What proportion of outpatients in a department of neurology suffers from medically unexplained symptoms, especially pain? What characteristics have good discriminative value in distinguishing medically explained *versus* medically unexplained symptoms?
2. Is the diagnosis of CUP reliable, or is it common that a medical explanation for pain is discovered at follow-up?
3. What are the determinants of pain severity and health-related quality of life in CUP?
4. Which clinical characteristics are useful in predicting future pain severity and health-related quality of life in CUP?

Part II: Pathophysiology: pain sensitivity and cerebral pain processing

5. How does the somatosensory profile, especially pain sensitivity for different modalities, of CUP patients compare with the somatosensory profile of healthy persons?
6. What is the influence of attention towards pain (*versus* distraction from pain) on subjective pain intensity in CUP?
7. Does cerebral pain processing during distraction in CUP differ from physiological cerebral pain processing?
8. Are abnormalities in pain sensitivity and pain processing in CUP limited to clinically affected body regions or are they spatially generalized?

Part I: Epidemiology

The global aim of part I of this thesis is to assess the prevalence and characteristics of CUP and other unexplained symptoms, and to determine whether certain clinical characteristics are related to present and future severity of CUP.

Chapter 2 focuses on the prevalence and clinical predictors of medically unexplained symptoms, including unexplained pain, in an academic neurology outpatient clinic. The reliability of the diagnosis 'CUP' is the subject of **chapter 3**, in which we studied the frequency of new diagnoses that explain pain symptoms during the follow-up of a large cohort of CUP patients. In this same cohort, we describe the clinical characteristics and present a cross-sectional analysis for determinants of pain severity and health-related quality of life (**chapter 4**). **Chapter 5** focuses on the follow-up of this CUP cohort, with the aim of identifying predictors of health-related quality of life and pain decrease.

Part II: Pathophysiology: pain sensitivity and cerebral pain processing

The overall aim of this part is to increase understanding of pathophysiological processes underlying CUP at the subjective level (pain sensitivity and experience) as well as the level of brain function.

In **chapter 6**, a large group of CUP patients is compared with healthy subjects in their somatosensory profile (sensitivity to painful and non-painful stimuli of different modalities) by means of quantitative sensory testing. Given the established role of attention on cerebral pain processing, **chapter 7** describes a psychophysical study on the relation between attention and subjective pain intensity in CUP patients and healthy subjects. Finally, we present the results of a functional MRI study on cerebral pain processing during distraction in CUP *versus* healthy volunteers (**chapter 8**).

In summary, our understanding of the clinical characteristics and pathophysiology of CUP is still limited. In particular, it is unclear which mechanisms connect psychological and sociodemographic risk factors with clinical pain. Through study at the clinical as well as the pathophysiological level, we aim to increase the understanding of CUP from a biopsychosocial perspective. This thesis has the long-term goal of opening gateways towards novel treatment strategies, but its results may also be of immediate clinical use, as clinicians may use new insights on the diagnosis and background of CUP in their communication with patients.

REFERENCES

1. Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? Lancet 1999;354:936-9.
2. Crimlisk HL, Bhatia K, Cope H, David A, Marsden CD, Ron MA. Slater revisited: 6 year follow up study of patients with medically unexplained motor symptoms. BMJ 1998;316:582-6.
3. Stone J, Carson A, Duncan R, Coleman R, Roberts R, Warlow C, et al. Symptoms 'unexplained by organic disease' in 1144 new neurology out-patients: how often does the diagnosis change at follow-up? Brain 2009;132:2878-88.
4. Stone J, Smyth R, Carson A, Warlow C, Sharpe M. La belle indifference in conversion symptoms and hysteria: systematic review. Br J Psychiatry 2006;188:204-9.
5. Hamilton J, Campos R, Creed F. Anxiety, depression and management of medically unexplained symptoms in medical clinics. J R Coll Physicians Lond 1996;30:18-20.
6. Leiknes KA, Finset A, Moum T, Sandanger I. Course and predictors of medically unexplained pain symptoms in the general population. J Psychosom Res 2007;62:119-28.
7. Stone J, Wojcik W, Durrance D, Carson A, Lewis S, MacKenzie L, et al. What should we say to patients with symptoms unexplained by disease? The "number needed to offend". British Medical Journal 2002;325:1449-50.
8. Henningsen P, Zipfel S, Herzog W. Management of functional somatic syndromes. Lancet 2007;369:946-55.
9. Part III: Pain Terms, A Current List with Definitions and Notes on Usage. In: IASP Task Force on Taxonomy, Merskey H, Bogduk N, editors. Classification of Chronic Pain. 2nd edition ed. Seattle: IASP Press; 1994. p. 209-14.
10. Loeser JD, Black RG. A taxonomy of pain. Pain 1975;1:81-4.
11. Mayou R, Kirmayer LJ, Simon G, Kroenke K, Sharpe M. Somatoform disorders: time for a new approach in DSM-V. Am J Psychiatry 2005;162:847-55.
12. Edwards RR, Bingham CO, III, Bathon J, Haythornthwaite JA. Catastrophizing and pain in arthritis, fibromyalgia, and other rheumatic diseases. Arthritis Rheum 2006;55:325-32.
13. Lipowski ZJ. Somatization - the concept and its clinical application. American Journal of Psychiatry 1988;145:1358-68.
14. Mayer EA, Bushnell MC. Functional Pain Syndromes: Presentation and Pathophysiology. Seattle, WA: IASP press; 2009.
15. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994;121:953-9.
16. [1990 classification criteria of fibromyalgia from the American College of Rheumatology. Report of the Multicenter Criteria Committee]. Union Med Can 1990;119:272.
17. Aaron LA, Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. Ann Intern Med 2001;134:868-81.

18. Nimnuan C, Rabe-Hesketh S, Wessely S, Hotopf M. How many functional somatic syndromes? J Psychosom Res 2001;51:549-57.

19. Linton SJ. A review of psychological risk factors in back and neck pain. Spine (Phila Pa 1976) 2000;25:1148-56.

20. Weir PT, Harlan GA, Nkoy FL, Jones SS, Hegmann KT, Gren LH, et al. The incidence of fibromyalgia and its associated comorbidities: a population-based retrospective cohort study based on International Classification of Diseases, 9th Revision codes. J Clin Rheumatol 2006;12:124-8.

21. Pincus T, Burton AK, Vogel S, Field AP. A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. Spine (Phila Pa 1976) 2002;27:E109-E120.

22. Pfau DB, Rolke R, Nickel R, Treede RD, Daublaender M. Somatosensory profiles in subgroups of patients with myogenic temporomandibular disorders and Fibromyalgia Syndrome. Pain 2009;147:72-83.

23. Sterling M, Jull G, Vicenzino B, Kenardy J. Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery. Pain 2003;104:509-17.

24. McDermid AJ, Rollman GB, McCain GA. Generalized hypervigilance in fibromyalgia: evidence of perceptual amplification. Pain 1996;66:133-44.

25. Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, et al. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain 2004;127:835-43.

26. Baliki MN, Chialvo DR, Geha PY, Levy RM, Harden RN, Parrish TB, et al. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. J Neurosci 2006;26:12165-73.

27. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011;152:S2-15.

28. Mayer EA, Bushnell MC. Functional pain disorders: time for a paradigm shift? In: Mayer EA, Bushnell MC, editors. Functional pain syndromes. 1st ed. Seattle: IASP Press; 2009. p. 531-65.

29. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain 2006;10:287-333.

30. Nimnuan C, Hotopf M, Wessely S. Medically unexplained symptoms - An epidemiological study in seven specialities. Journal of Psychosomatic Research 2001;51:361-7.

31. Carson AJ, Ringbauer B, Stone J, MacKenzie L, Warlow C, Sharpe M. Do medically unexplained symptoms matter? A prospective cohort study of 300 new referrals to neurology outpatient clinics. J Neurol Neurosurg Psychiatry 2000;68:207-10.

32. Verhaak PFM, Kerssens JJ, Dekker J, Sorbi MJ, Bensing JM. Prevalence of chronic benign pain disorder among adults: a review of the literature. Pain 1998;77:231-9.

33. McBeth J, Jones K. Epidemiology of chronic musculoskeletal pain. Best Pract Res Clin Rheumatol 2007;21:403-25.

34. Kerssens JJ, Verhaak PF, Bartelds AI, Sorbi MJ, Bensing JM. Unexplained severe chronic pain in general practice. Eur J Pain 2002;6:203-12.

35. Bannwarth B, Blotman F, Roue-Le LK, Caubere JP, Andre E, Taieb C. Fibromyalgia syndrome in the general population of France: a prevalence study. Joint Bone Spine 2009;76:184-7.

36. Hungin AP, Whorwell PJ, Tack J, Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. Aliment Pharmacol Ther 2003;17:643-50.

37. Stone J, Smyth R, Carson A, Lewis S, Prescott R, Warlow C, et al. Systematic review of misdiagnosis of conversion symptoms and "hysteria". BMJ 2005;331:989.

38. Smith BH, Macfarlane GJ, Torrance N. Epidemiology of chronic pain, from the laboratory to the bus stop: time to add understanding of biological mechanisms to the study of risk factors in population-based research? Pain 2007;127:5-10.

39. Fransen M, Woodward M, Norton R, Coggan C, Dawe M, Sheridan N. Risk factors associated with the transition from acute to chronic occupational back pain. Spine 2002;27:92-8.

40. Karjalainen K, Malmivaara A, Mutanen P, Pohjolainen T, Roine R, Hurri H. Outcome determinants of subacute low back pain. Spine 2003;28:2634-40.

41. Campbell LC, Clauw DJ, Keefe FJ. Persistent pain and depression: A biopsychosocial perspective. Biological Psychiatry 2003;54:399-409.

42. Fillingim RB, Ohrbach R, Greenspan JD, Knott C, Dubner R, Bair E, et al. Potential psychosocial risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. J Pain 2011;12:T46-T60.

43. Sterling M, Jull G, Vicenzino B, Kenardy J, Darnell R. Physical and psychological factors predict outcome following whiplash injury. Pain 2005;114:141-8.

44. Lillefjell M, Krokstad S, Espnes GA. Prediction of function in daily life following multidisciplinary rehabilitation for individuals with chronic musculoskeletal pain; a prospective study. BMC Musculoskelet Disord 2007;8:65.

45. Teasell RW. Compensation and chronic pain. Clin J Pain 2001;17:S46-S64.

46. Engel GL. The need for a new medical model: a challenge for biomedicine. Science 1977;196:129-36.

47. Nielson WR, Weir R. Biopsychosocial approaches to the treatment of chronic pain. Clin J Pain 2001;17:S114-S127.

48. Jensen TS, Baron R. Translation of symptoms and signs into mechanisms in neuropathic pain. Pain 2003;102:1-8.

49. Treede RD, Baron R. How to detect a sensory abnormality. Eur J Pain 2008;12:395-6.

50. Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. J Pain 2009;10:556-72.

51. Peyron R, Garcia-Larrea L, Gregoire MC, Costes N, Convers P, Lavenne F, et al. Haemodynamic brain responses to acute pain in humans: sensory and attentional networks. Brain 1999;122 (Pt 9):1765-80.

52. Crombez G, Eccleston C, Van den Broeck A, Goubert L, Van Houdenhove B. Hypervigilance to pain in fibromyalgia: the mediating role of pain intensity and catastrophic thinking about pain. Clin J Pain 2004;20:98-102.

53. Veldhuijzen DS, Kenemans JL, van Wijck AJ, Olivier B, Kalkman CJ, Volkerts ER. Processing capacity in chronic pain patients: a visual event-related potentials study. Pain 2006;121:60-8.

54. Loeser JD, IASP Taxonomy Working Group. IASP Pain Terminology. http://www.iasp-pain org/Content/NavigationMenu/GeneralResourceLinks/PainDefinitions/default.htm 2011 July 14 [visited 2012 Feb 19].

55. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature 1983;306:686-8.

56. Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965;150:971-9.

57. Arendt-Nielsen L, Henriksson KG. Pathophysiological mechanisms in chronic musculoskeletal pain (fibromyalgia): the role of central and peripheral sensitization and pain disinhibition. Best Pract Res Clin Rheumatol 2007;21:465-80.

58. Rollman GB, Lautenbacher S. Hypervigilance effects in fibromyalgia: pain experience and pain perception. In: Værøy H, Merskey H, editors. Progress in fibromyalgia and myofascial pain. 1st ed. Amsterdam: Elsevier; 1993. p. 283-309.

59. Hollins M, Harper D, Gallagher S, Owings EW, Lim PF, Miller V, et al. Perceived intensity and unpleasantness of cutaneous and auditory stimuli: an evaluation of the generalized hypervigilance hypothesis. Pain 2009;141:215-21.

60. Peters ML, Vlaeyen JW, van Drunen C. Do fibromyalgia patients display hypervigilance for innocuous somatosensory stimuli? Application of a body scanning reaction time paradigm. Pain 2000;86:283-92.

61. Ramsey NF, Hoogduin H, Jansma JM. Functional MRI experiments: acquisition, analysis and interpretation of data. Eur Neuropsychopharmacol 2002;12:517-26.

62. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005;9:463-84.

63. Legrain V, Iannetti GD, Plaghki L, Mouraux A. The pain matrix reloaded: a salience detection system for the body. Prog Neurobiol 2011;93:111-24.

64. Mouraux A, Diukova A, Lee MC, Wise RG, Iannetti GD. A multisensory investigation of the functional significance of the "pain matrix". Neuroimage 2011;54:2237-49.

65. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron 2007;55:377-91.

66. Bantick SJ, Wise RG, Ploghaus A, Clare S, Smith SM, Tracey I. Imaging how attention modulates pain in humans using functional MRI. Brain 2002;125:310-9.

67. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002;46:1333-43.

68. Kwan CL, Diamant NE, Pope G, Mikula K, Mikulis DJ, Davis KD. Abnormal forebrain activity in functional bowel disorder patients with chronic pain. Neurology 2005;65:1268-77.

69. Napadow V, Lacount L, Park K, As-Sanie S, Clauw DJ, Harris RE. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. Arthritis Rheum 2010.

70. Baliki MN, Baria AT, Apkarian AV. The cortical rhythms of chronic back pain. J Neurosci 2011;31:13981-90.

71. Tracey I, Ploghaus A, Gati JS, Clare S, Smith S, Menon RS, et al. Imaging attentional modulation of pain in the periaqueductal gray in humans. J Neurosci 2002;22:2748-52.

PART I

Epidemiology

2

Prevalence and predictors of unexplained neurological symptoms in an academic neurology outpatient clinic: An observational study

Tom J. Snijders
Frank-Erik de Leeuw
Ursula M. H.Klumpers
L. Jaap Kappelle
Jan van Gijn

J Neurol 2004;251:66-71

ABSTRACT

Objectives: (a) To determine the prevalence of unexplained symptoms among newly referred patients in a Dutch academic outpatient clinic for general neurology; (b) To identify factors that can serve as characteristics and possibly as screening instruments for unexplained symptoms in this population.

Methods: Observational study, consisting of self-assessment questionnaires. Patients and resident neurologists completed self-designed questionnaires, which included questions about possible features of unexplained symptoms. Patients also completed the Hospital Anxiety and Depression Scale (HADS), evaluating the existence of anxiety and depressive symptoms. Diagnosis of unexplained symptoms was based on the final classification of the patient's symptoms as non-organic, after assessment by a senior neurologist. In the analysis, separate predicting factors and groups of factors were adjusted for age, sex and HADS-score, and analyzed as possible characteristics of unexplained symptoms.

Results: 35% of the patients (208 total, 174 completed questionnaires) were considered to suffer from unexplained symptoms. Young age ($p<0.001$) and female sex ($p=0.007$) were significantly associated with unexplained symptoms, high HADS scores were not ($p=0.10$). Characteristics associated with unexplained symptoms were the resident's preliminary impression of symptoms being non-organic, after reading of the referral letter [OR 96.8, 95% confidence interval (95% CI) 29.7–315, PPV 82%, NPV 96%] and after the first encounter (OR 305, 95% CI 37.3–2494.6, PPV 83%, NPV 98%), but before the actual history taking and neurological examination. The only other non-demographic characteristic of unexplained symptoms was a visit in order to obtain a second opinion (OR 2.43, 95% CI 1.15–5.10). Clustering of these factors, however, did not have sufficient predictive power to result in an accurate screening instrument.

Conclusions: Unexplained symptoms are common in the neurology outpatient clinic and are to some extent predicted by the physician's preliminary judgment of symptoms. However, history taking and neurological examination remain indispensable for the detection of less obvious organic disorders.

INTRODUCTION

Unexplained symptoms are common in all fields of medicine. They form a widespread problem which imposes a large burden upon patients and health care providers, from a professional as well as from a financial point of view. Health care costs in patients with multiple unexplained symptoms are up to nine times higher than in the general population.[1] The phenomenon of medically unexplained symptoms, as well as the associated concept of somatization and many symptom clusters of unexplained origin (e. g. fibromyalgia), is the subject of lively scientific discussion,[2,3] and a wide variety of studies.[4-8]

Since (pseudo)neurological symptoms are common among these patients, neurologists are often confronted with them. Previous studies in neurological patients found that 24–40% of all patients have symptoms that cannot fully be explained by a neurological or any other organic disease, both in hospitalized patients,[5,6] and in outpatients.[4,8]

Early detection of unexplained symptoms in these patients may create possibilities for simple yet effective management strategies,[9] and in this way contribute to the patient's well-being. In addition, early detection may reduce the burden posed upon the health care system.[7] However, there are few effective diagnostic tools for the early detection of unexplained symptoms.

Our study had two aims. Firstly, we wanted to determine the prevalence of unexplained symptoms among patients who were newly referred to an academic general neurology outpatient clinic in the Netherlands. Secondly, we studied the association between the final diagnosis of unexplained symptoms and characteristics of the patient's medical history and social environment, and aspects of the referral and the consultation. We also evaluated the usefulness of these variables as diagnostic tools in the detection of unexplained symptoms.

PATIENTS AND METHODS

Patients

The study population consisted of all consecutive patients that were newly referred to the general neurology outpatient clinic of the University Medical Centre Utrecht, The Netherlands in March-April 2000 (n=208). None of them refused to participate in this study. A resident neurologist first examined these patients. A senior neurologist supervised all consultations. The medical research ethics committee of the University Medical Centre of Utrecht, The Netherlands, approved the study.

Measurement of unexplained symptoms

We defined the diagnosis of unexplained symptoms by means of the clinician's classification of symptoms as 'not organic'. This final classification of the patient's symptoms as organic or not organic by the resident neurologist, the so-called 'organicity rating', took place at the end of the entire consultation which went from reading the referral letter, history taking and the neurological examination to consultation with a supervising senior neurologist (who would usually see the patient as well). The category 'organic' included not only structural diseases of the nervous system or musculature, but also well recognized functional syndromes such as trigeminal neuralgia and spasmodic torticollis, and non-neurological (e.g. orthopedic) organic disease conditions. Furthermore, it included diseases and syndromes with (partially) unresolved causes, where an organic cause is commonly assumed, e.g. multiple sclerosis. The category 'not organic' included symptoms that could not be explained by current neurological insights as well as complaints of presumed psychological origin, even if an intermediate somatic factor might be part of its pathophysiology (e.g. increased muscle tone in tension headache). This resulted in a heterogeneous group of 'non-organic' symptoms, such as back pain irradiating to the legs but without signs of radicular compression, conversion syndromes and pain that 'moves' from one region to the other.

Putative characteristics of unexplained symptoms

Both the patient (appendix A) and the resident neurologist (appendix B) completed a questionnaire designed for the purpose of this study which included possible characteristics of unexplained symptoms. These items were the reason for referral, the patient's medical history and social environment and several aspects of the consultation. We asked the residents about their impression of the symptoms (organic or non-organic) at two different moments before the actual consultation: (a) after reading the referral letter, but before meeting the patient; (b) on the first encounter with the patient. The residents completed these questions about the initial appraisal of symptoms before the actual consultation (history and neurological examination) took place. Patients filled out their questionnaires without a physician or student being present, after the history taking and neurological examination, while the resident was relating the history and examination to the supervising neurologist.

Thirty-four of the 208 questionnaires were incomplete, i.e. we did not receive a completed questionnaire from either the patient or the resident neurologist. The reasons were: the questionnaire was lost (12 questionnaires); practical problems for the patient such as not having reading glasses, lack of time or language problems (8 questionnaires); other reasons or reason unknown (14 questionnaires). The other 174 questionnaires (84%) were available for analysis.

Measurement of anxiety and depressive symptoms

The relation between a given characteristic and unexplained symptoms may be confounded by anxiety and depressive symptoms, since these are common among patients with unexplained symptoms.[10] To assess the presence of these symptoms, patients completed the Hospital Anxiety and Depression Scale (HADS), a well-validated self assessment scale for use in an outpatient clinic.[11,12] A total HADS score above 14 is considered to reflect the existence of anxiety or depressive symptoms.

Statistical analysis

We calculated the age- and sex-specific prevalence of unexplained symptoms by means of χ^2 test and ANOVA, respectively. We quantified the association between possible characteristics of unexplained symptoms and the final diagnosis of unexplained symptoms by means of odds ratios (ORs) with a 95% confidence interval (95% CI). In order to avoid confounding the association between the resident's initial impressions on the nature of symptoms and the final diagnosis of unexplained symptoms, we stratified the analysis by first or second opinion visits.

In order to try and develop a diagnostic tool for unexplained symptoms, we calculated the positive and negative predictive value (PPV and NPV), the sensitivity and specificity of the questions in appendices A and B for unexplained symptoms.

Since the existence of unexplained symptoms might be more closely associated with a combination of factors rather than with a single factor, we combined those questions in the questionnaire for resident physicians and that for patients with the highest four ORs of all items (but with exclusion of the questions about the residents' early judgments, since these cannot be generalized). For this set of questions, we subsequently calculated a receiver operator characteristic (ROC)-curve. From this curve we obtained the number of positively answered questions with the highest value as a screening tool for unexplained symptoms. Sensitivity, specificity, PPV and NPV of this combination of positive answers were also calculated.

All data were entered and analyzed in SPSS for Windows. All analyses were adjusted for age, sex and anxiety and depressive symptoms.

RESULTS

Demographics and prevalence of unexplained symptoms

Mean age in the patient group was 48.5 years (SD 16.9, range 17–86) and 62% of them was female. Most patients visited the outpatient clinic for a second opinion (51%).

Eventually, 35% of patients were judged to suffer from unexplained symptoms. Type and location of symptoms are summarized in table 2.1. Fifty-nine percent of all participants had symptoms with a presumed organic cause (neurological or otherwise). In the remaining 6%, the physicians were not certain whether the complaints were organic or not. Unexplained symptoms were significantly associated with female sex (p=0.007) and with young age, especially age under 40 (p<0.001) (table 2.2).

Table 2.1 Unexplained symptoms by type and location*

Type of symptom	Frequency (%)	Location of symptom	Frequency (%)
Pain	43.1	Head / Neck	26.2
Non-painful sensory symptoms	10.8	Limbs	16.9
Weakness	4.6	Back (+ irradiating to lower limb(s))	20.0
Dizziness and disturbance of equilibrium and consciousness	4.6	Multiple locations	15.4
Other	4.6	Generalized	4.6
Multiple symptoms	26.2	No location**	13.8
No complaint / Fear of disease	3.1	Unknown	3.1
Unknown	3.1		

* Only the unexplained symptoms of patients with complete questionnaires are included (n=65).
** e.g. change in behaviour, fear of disease.

Table 2.2 Frequency of unexplained symptoms by sex and age. Patients with an organicity rating of 'not sure' were excluded from this analysis.

		Organicity rating (%)	
		Organic	Non-organic
Sex	Male	74.3	25.7
	Female	54.8	45.2*
Age	< 40	41.5	58.5**
	40 – 59	60.6	39.4
	> 59	88.0	12.0
Overall		62.6	37.4

* $p = 0.007$ (χ^2 test)
** $p < 0.001$ (ANOVA)

Possible characteristics

The resident's judgment of symptoms as non-organic after reading the referral letter, but before actually meeting the patient, and a similar judgment immediately after the first encounter with the patient, were both strongly related to the final diagnosis of unexplained symptoms [OR 96.8 (95% CI 29.7–315.4), and OR 305.0 (95% CI 37.3–2494.6), respectively]. Stratification by first specialist referrals or second opinion consultations did not alter this association.

There was a relatively high rate of unexplained symptoms in patients who visited the clinic for a second opinion (OR 2.2, 95% CI 1.1–4.2). The use of more than one type of medication (regardless of type of medication) was also significantly related to unexplained symptoms (OR 3.2, 95% CI 1.2–8.8).However, after adjustment for HADS-score, this association was no longer significant (2.3, 95% CI 0.8–6.8).

Diagnostic tools

In keeping with the ORs, strong diagnostic tools for unexplained symptoms were the resident's early judgments of symptoms as non-organic: after reading the referral letter, but before meeting the patient (sensitivity 93%, specificity 88%, PPV 82%, NPV 96%), and at the first encounter with the patient (sensitivity 98%, specificity 87%, PPV 83%, NPV 98%). None of the other individual questions (appendices A and B) proved to be a useful diagnostic tool for unexplained symptoms. Combining the individual questions with the highest four ORs, as marked in the appendices, (but with exclusion of the initial impressions) did not result in a more powerful diagnostic test for the identification of unexplained symptoms than was the case for separate questions.

Anxiety and depressive disorder

Of all patients, 31% had anxiety or depressive symptoms. Unexplained symptoms were not significantly related to high mean HADS scores (11 vs. 10, p=0.22) or to a higher rate of HADS-scores above the cut-off point for anxiety or depressive symptoms (32.2% vs. 27.7%, p=0.34) than in patients with symptoms of presumably organic origin. With the exception of one characteristic (use of more than one type of medication, see above), stratification by HADS-score did not markedly alter the magnitude of the associations between unexplained symptoms and the characteristics and diagnostic tools.

DISCUSSION

Just over one third of all newly referred patients in our general neurology outpatient clinic were considered to suffer from unexplained symptoms, with a higher prevalence in women and patients under the age of 40. In accordance with their highly subjective nature, sensory symptoms, especially pain, constituted the majority of all unexplained symptoms. We found no significant association between anxiety or depressive symptoms and unexplained symptoms. The resident's early judgments of symptoms as non-organic (after reading the referral letter and at the first encounter with the patient) were strong, but not entirely accurate predictors of unexplained symptoms. Referral for a second opinion also proved to be a significant characteristic of unexplained symptoms.

Methodological aspects

Some methodological aspects of this study need to be considered. The study population is a selected group. Many patients had been examined by several physicians (general physicians and/or specialists) before they visited an academic outpatient clinic. Not all patients with unexplained symptoms demonstrate a sufficient degree of illness behavior to go on seeking more medical attention, up to this level. Furthermore, since this study was performed in a general neurology outpatient clinic, certain groups of patients were underrepresented because they are referred to more specialized outpatient clinics, e.g. for neuromuscular diseases. No data are available on the prevalence of unexplained symptoms in sub-specialty neurology outpatient clinics, or on the differences in prevalence of unexplained symptoms between academic and non-academic outpatient clinics. Therefore, the effect of these two types of selection bias on our results cannot be reliably estimated. However, since a large number of patients were included and none of them refused to participate, the study population seems to be a true reflection of a population at a Dutch academic general neurology outpatient clinic.

Conceptual issues

Unexplained symptoms form a key element of several conceptually and clinically overlapping syndromes and disorders such as somatization, psychogenic complaints and DSM-IV somatoform disorders.[2] Somatization as defined by Lipowski shows the closest resemblance to the type of symptoms we studied. In this definition, somatization is a tendency to experience and communicate somatic distress and symptoms unaccounted for by pathological findings, to attribute these symptoms to physical illness and to seek medical help for them.[3] However, somatization can be a misleading term because of its complexity and the many different

interpretations.[2] We use the term '(medically) unexplained symptoms' because it does not imply any assumptions about underlying psychological or other causal factors.

Diagnosis of unexplained symptoms

We considered the clinician's final judgment of the nature of the presented symptom, after history taking, neurological examination and consultation of a senior neurologist, as the most adequate criterion for diagnosing unexplained symptoms for the purpose of this study, as was previously done in similar studies.[4-6] With this method of assessment, there is a risk of missing the diagnosis of an organic (neurological or non-neurological) disease. However, this is only the case in a very limited number of cases. This is in agreement with a previous study, in which all patients with a diagnosis of 'unexplained symptoms' (as rated at the initial consultation) had an unchanged organicity rating at 8 month follow up.[13] Our results also correspond well with earlier studies in that they consistently report a prevalence of non-organic symptoms in about 30–40% of the patients, in different types of neurology clinics.[4-6,8]

Characteristics and diagnostic tools

The resident's early judgments of symptoms as non-organic were the strongest predicting characteristics of unexplained symptoms. In our outpatient clinic, all consultations are preceded by a referral letter from the family physician or from another specialist. Apparently, the medical information in this referral letter provides the resident neurologist with a strong though not infallible impression of the nature of a patient's symptoms. Further maturation of this impression takes place at the first encounter with the patient, which informs the physician about the patient through his appearance, behavior, psychomotor activity and attitude towards the physician.[14] Of the other characteristics we studied, only consultation for a second opinion was a significant characteristic.

That we could not construct an accurate diagnostic tool for the diagnosis of 'unexplained symptoms' from a combination of characteristics (with exclusion of the early judgments, because this cannot be projected to other situations) supports the hypothesis that this diagnosis is not dependent on a single factor. Rather, it is the integrated result of the clinical impression from the referral letter and the first encounter, the formal history, the neurological examination, and the final evaluation by a consultant physician. However, the referral letter and the first encounter already provide enough information to suspect the diagnosis of unexplained symptoms with moderate certainty.

Anxiety and depressive disorder

The lack of a statistically significant association between anxiety and depressive symptoms on the one hand and unexplained symptoms on the other is in contradiction with previous studies.[4,10,15] It might be explained by our use of a self-assessment scale (HADS) in the evaluation of anxiety and depressive symptoms, instead of using a structured clinical interview for psychiatric disorders, according to DSM-IV-criteria (e.g. SCID I-interview).[4,15] Nevertheless, we found a trend similar to these previous studies. Therefore, it is still worthwhile considering a psychiatric consultation in any patient with unexplained physical symptoms and features of anxiety or depressive disorder.

CONCLUSION

A large proportion of patients in the academic general neurology outpatient clinic presents with unexplained symptoms. We did not demonstrate a significant association between such symptoms and symptoms of anxiety or depression. The best screening instrument seems to be the physician's pre-consultation judgment of the nature of symptoms, based on the referral letter and the first encounter with the patient. However, the predictive value of these and other screening instruments was insufficiently accurate to entirely exclude organic disease. A full history and neurological examination remain indispensable to identify patients with uncommon organic disorders.

By early identification of unexplained symptoms, the physician can prevent unnecessary involvement of the patient in numerous investigative procedures. Preferably, treatment or referral should be aimed at the patient's ideas about illness, his diminished social and occupational functioning, and co-existing psychiatric morbidity.

ACKNOWLEDGEMENTS

We thank A. M. van Hemert, Dept. of Psychiatry, University Medical Centre of Leiden, The Netherlands, for his advice, and the residents in neurology and the patients in the General Neurology outpatient clinic of the University Medical Centre of Utrecht, The Netherlands, for their participation.

REFERENCES

1. Smith GR, Jr., Monson RA, Ray DC. Patients with multiple unexplained symptoms. Their characteristics, functional health, and health care utilization. Arch Intern Med 1986;146:69-72.
2. De Gucht V, Fischler B. Somatization: a critical review of conceptual and methodological issues. Psychosomatics 2002;43:1-9.
3. Lipowski ZJ. Somatization - the concept and its clinical application. American Journal of Psychiatry 1988;145:1358-68.
4. Carson AJ, Ringbauer B, Stone J, MacKenzie L, Warlow C, Sharpe M. Do medically unexplained symptoms matter? A prospective cohort study of 300 new referrals to neurology outpatient clinics. J Neurol Neurosurg Psychiatry 2000;68:207-10.
5. Creed F, Firth D, Timol M, Metcalfe R, Pollock S. Somatization and illness behaviour in a neurology ward. J Psychosom Res 1990;34:427-37.
6. Ewald H, Rogne T, Ewald K, Fink P. Somatization in patients newly admitted to a neurological department. Acta Psychiatr Scand 1994;89:174-9.
7. van Gijn J, Bierman WF, Zuketto C, Rooijmans HG. Chronische, onverklaarde pijn: van klacht naar doel. Ned Tijdschr Geneeskd 2000;144:641-4.
8. Perkin GD. An analysis of 7836 successive new outpatient referrals. J Neurol Neurosurg Psychiatry 1989;52:447-8.
9. Price JR. Managing physical symptoms: the clinical assessment as treatment. J Psychosom Res 2000;48:1-10.
10. Hamilton J, Campos R, Creed F. Anxiety, depression and management of medically unexplained symptoms in medical clinics. J R Coll Physicians Lond 1996;30:18-20.
11. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997;27:363-70.
12. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.
13. Carson AJ, Best S, Postma K, Stone J, Warlow C, Sharpe M. The outcome of neurology outpatients with medically unexplained symptoms: a prospective cohort study. Journal of Neurology Neurosurgery and Psychiatry 2003;74:897-900.
14. Kaplan HI, Sadock BJ. Clinical examination of the psychiatric patient. Synopsis of psychiatry. 8 ed. Baltimore: Williams & Wilkins; 1998. p. 240-74.
15. van Hemert AM, Hengeveld MW, Bolk JH, Rooijmans HG, Vandenbroucke JP. Psychiatric disorders in relation to medical illness among patients of a general medical out-patient clinic. Psychol Med 1993;23:167-73.

APPENDIX A Patient's questionnaire

1. Have you ever been diagnosed with fibromyalgia?*
2. Have you ever been diagnosed with a whiplash injury?
3. Have you ever been diagnosed with the chronic fatigue syndrome (ME)?
4. Have you ever had chronic tailbone pain (a. k. a. coccygodynia)?
5. Have you ever been diagnosed with the irritable bowel syndrome (IBS)?*
6. Did you have more than 1 abdominal operation in the past?
7. Have you ever been treated for a burnout, a depression or an anxiety disorder by a psychiatrist or psychologist?
8. Do you currently have a partner?
9. Does your current complaint have a negative effect on your social environment (work/ relationships)?
10. Do you currently take medication?
11. Do you take more than one type of medication?*

* Included in the group of questions which was evaluated for its value as a characteristic of and/or a diagnostic tool for unexplained symptoms

APPENDIX B Resident's questionnaire

1. Was your first impression after reading the letter of referral (but before meeting the patient and history taking), that the patient's complaint has an organic origin?[a]
2. Was your first impression of the patient, e.g. the manner of getting up from his/her chair in the waiting room, the way of walking and of making contact), that the patient's complaint has an organic origin?[b]
3. Did the patient use expedients (walker, cane, wheelchair etc.)?
4. Was another specialist already consulted for the same complaint?[c]
5. What was the reason of the 'second opinion'-visit?
6. Was the patient accompanied by someone (friend, partner, parent etc.)?
7. Did the patient bring a list of complaints, and did he/she use it during history taking?
8. Did you observe a discrepancy between the patient's limitations in daily activities and the deficits found during the neurological examination?
9. Did you observe any signs related to the complaint during the neurological exam?
10. Do you think that the present complaint has an organic origin, after history taking, neurological examination and consultation of the senior neurologist?[d]

[a] The resident answered this question after reading the referral letter, but before the first encounter with the patient.

[b] The resident answered this question after the first encounter with the patient, but before history taking and neurological examination.

[c] Included in the group of questions which was evaluated for its value as a characteristic of and/or a diagnostic tool for unexplained symptoms.

[d] This question is referred to as the 'organicity rating'.

3

Misdiagnosis of chronic, unexplained pain: a follow-up study

Sjoerd Kruis
Tom J. Snijders
Jan van Gijn

Submitted for publication

ABSTRACT

Background: Medically unexplained symptoms (MUS) are common in Neurology and most other medical specialties and often include unexplained pain. Unexplained symptoms often cause a feeling of uncertainty for physicians and patients whether an underlying organic disease is 'missed'. Recent literature argues against a high rate of misdiagnosis in MUS, but this was never separately studied in chronic, unexplained pain (CUP).

Methods: We performed a follow-up study on patients presenting with pain symptoms labeled as CUP at the Neurology, Pain Medicine or Rheumatology outpatient clinics in two different hospitals. At baseline, sociodemographic data were recorded and patients completed the Hospital Anxiety and Depression Scale. At 16-month follow-up we asked all patients whether a new disease, explaining pain at inclusion, had been diagnosed since baseline; if so, we evaluated medical records to confirm the new diagnosis. We performed exploratory analysis to find predictors for the occurrence of a new diagnosis.

Results: Of the 422 patients included at baseline, 274 (65%) returned the follow-up questionnaire. In this last group of patients we indentified 4 cases of misdiagnosis (1.6%). This rate was comparable with rates from recent studies on MUS. We did not find any significant predictors for a new diagnosis, which may (partly) be due to the small number of events.

Conclusions: We found a small proportion of misdiagnoses in CUP patients. This finding puts the uncertainty of a possible missed organic disease in CUP patients into a proper perspective.

INTRODUCTION

Medically unexplained symptoms (MUS) form a common problem in most medical specialties, general medical practice and the general population.[1,2] Many patients with MUS present with pain. In two studies on new neurology outpatients, pain is reported at a frequency of 31 and 43% of all patients with MUS.[3,4]

Physicians often find patients with MUS difficult to manage.[5] This difficulty lies, in part, in the degree of uncertainty for both the physician and the patient whether the unexplained symptoms, are not actually attributable to a 'missed' organic disorder. A frequently cited 1960s paper by Slater et al. gave food to this feeling of uncertainty, because it reported high rates (33%) of organic disease at follow-up of patients initially diagnosed with "hysteria".[6] A recent systematic review, however, reported frequencies ranging from 2% to 36%,[7] with lower rates of misdiagnosis (2%-6%) in the most recent studies (1980s and 1990s). The largest study to date showed absolute misdiagnosis in only 4 of 1144 patients (0.3%) initially diagnosed as having MUS.[3] In that study 355 patients presented with pain, of whom 2 (0.6%) turned out to have a missed diagnosis.

Previous studies focused on MUS as a group. The rate of misdiagnosis for different subgroups within the heterogeneous population of MUS patients is currently unknown. Therefore we aimed to study the frequency and predictors of misdiagnosis in patients with chronic, unexplained pain (CUP).

PATIENTS AND METHODS

As part of a prospective cohort study on CUP, we included patients in two hospitals (one academic and one large general) in the Netherlands. The local medical ethics committee of the two involved centers approved the study, in accordance with the Declaration of Helsinki (2008).

We consecutively screened patients newly referred to the Neurology, Pain Medicine or Rheumatology outpatient clinics for eligibility. Criteria for inclusion were:

- Adult patients (18 years or older) with pain symptoms lasting at least three months;
- No medical cause could be determined on standard medical evaluation. This included history taking and physical examination in all cases; ancillary investigations were performed at the discretion of the treating physician. Patients whose symptoms were labeled as a functional pain syndrome (e.g. fibromyalgia or non-specific low back pain) were included, since these syndromes are characterized by (chronic) pain in the absence of a conventional medical cause;[8] however, such a diagnostic label was not necessary for inclusion;
- Sufficient knowledge of the Dutch language.

If the treating physician and the study team agreed on eligibility, the patient was asked to participate. In case of patient permission, we retrieved the following information:

- Age, gender, current pain diagnosis and/or current functional pain syndrome, from medical records;
- The Hospital Anxiety and Depression Scale (HADS), Dutch version,[9,10] containing two 7-item scales: one for anxiety and one for depression, both with a score range of 0-21. We calculated the total HADS score as a compound measure for anxiety and depression;
- Work status, including information on sick leave and disability compensation from a self-designed questionnaire.

In case of non-response, we sent up to two reminders.

Fifteen to 16 months after inclusion we sent patients a self-designed questionnaire in which we asked them whether a physician found a new diagnosis since inclusion and if so, which diagnosis. In case the patient reported a new diagnosis, we requested and reviewed the patient's recent medical records and classified the reported new diagnosis into one of the following categories: "No new diagnosis explaining pain at inclusion", "Yes, new diagnosis explaining pain at inclusion", "Unclear" or "New functional pain syndrome diagnosis". In our final analysis we categorized these last two classifications as "No new diagnosis explaining pain at inclusion", since a functional pain syndrome does not constitute a conventional (organic) cause for pain. Patients who did not respond after one reminder were considered lost to follow-up.

The primary outcome measure was the frequency of patients with a new diagnosis that explained pain at inclusion. We used Fisher's exact test to compare our results with those found recently by Stone et al.[3] We planned to perform multiple regression analysis to find baseline predictors for the finding of a new explaining diagnosis at follow-up. Since the number of events (missed diagnoses) turned out to be too small, we only performed exploratory univariable analyses: logistic regression analysis for continuous determinants (age, HADS score) and Fisher's exact test for categorical determinants (gender, outpatient clinic, financial compensation).

RESULTS

Out of 422 CUP patients who were included at baseline, 274 (65%) patients completed follow-up (figure 3.1). Median follow-up time was 16 months (interquartile range (IQR) 14-17 months).

Of the patients that were included at baseline, 69% were female. Mean age was 49.9 years (standard deviation 14.6). Neurology was the most common outpatient clinic of inclusion (64%), followed by Pain medicine (20%) and Rheumatology (16%). Twenty percent of patients

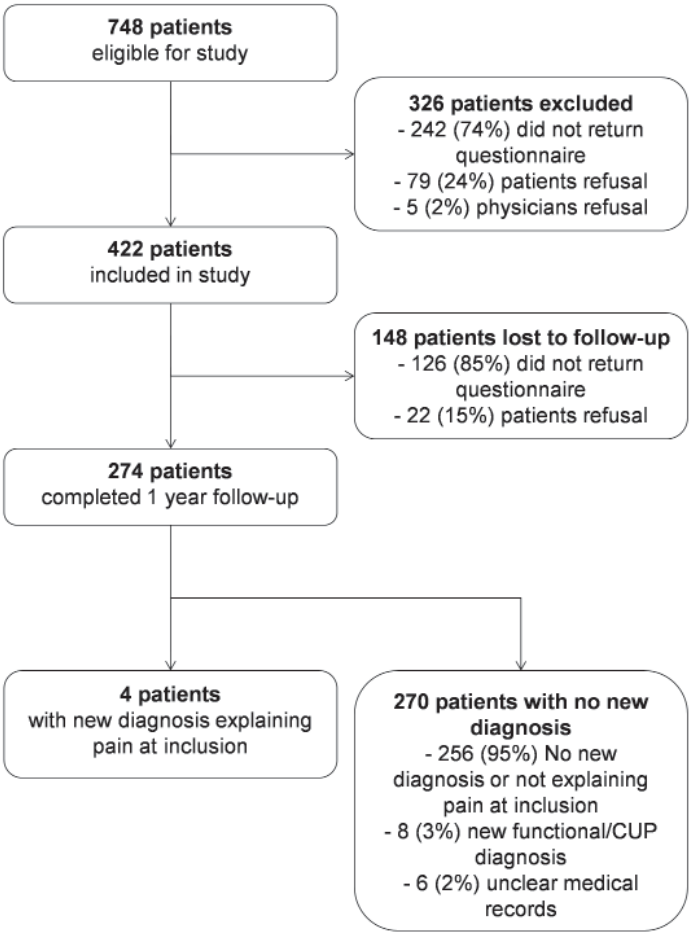

Figure 3.1 Flowchart of inclusion, follow-up and primary outcome.

received some sort of financial compensation in relation to their pain. Median HADS score was 12 (8-18). We found no significant differences in age, gender and department of inclusion between the baseline and follow-up sample.

At follow-up, 76 patients reported a new diagnosis. We obtained medical records of 52 patients. The medical records of the other 24 patients were not requested for the following reasons: no patient permission (12 patients); new diagnosis that clearly did not explain pain at inclusion, e.g. hypertension in a patient with low back pain (9); diagnosis was made by a non-medical person (3). After evaluating the 52 medical records, 4 patients (1.6%) had a confirmed new diagnosis that explained the pain at inclusion (figure 3.1); the cases are described in table 3.1. The frequency we found (1.6%) did not differ significantly from that found by Stone et al. in pain patients (p=0.41, Fisher's exact test).[3]

Table 3.1 Patients with a new diagnosis that explained pain at inclusion

Patient	Gender	Age (y)	Outpatient clinic of inclusion	Pain localization at inclusion	Diagnosis at follow-up	New diagnosis made by
Case 1	Male	66	Pain medicine	Both legs and back	Chronic idiopathic axonal (mainly sensory) polyneuropathy	Neurologist
Case 2	Male	62	Pain medicine	Headache	Common migraine	Neurologist
Case 3	Female	55	Neurology	Chronic widespread pain	Poly-arthrosis	Rheumatologist
Case 4	Female	48	Neurology	Left-sided low back pain	Lumbar spinal stenosis at L4 level	Neurosurgeon

Because there were only 4 misdiagnoses (events), our study was insufficiently powered to perform multiple regression analysis for baseline predictors of a new (missed) diagnosis. Instead we performed univariable analysis for 5 baseline variables: gender, age, outpatient clinic of inclusion, financial compensation status and total HADS-score. We did not find a significant association between any of these variables and the occurrence of a missed diagnosis at follow-up.

DISCUSSION

In this longitudinal study of the frequency of a new diagnosis in the follow-up of patients diagnosed with chronic, unexplained pain (CUP), we found a new diagnosis that, in retrospect, could explain the pain at inclusion in 4 out of 274 patients (1.6%). In the interpretation of medical records, we tended to classify cases with new diagnoses of uncertain but possible significance as 'new diagnosis that explained the pain at inclusion'; the rate of 1.6% therefore represents a liberal estimate.

The different types of MUS have many common characteristics and are often considered to form a single spectrum rather than separate entities;[11] still, this spectrum is heterogeneous. Pain is by definition subjective in nature and may give rise to specific difficulties in the diagnostic process. Clinicians who feel uncertain or uncomfortable in labeling pain as 'unexplained' may feel supported by the current data on diagnostic certainty since they are specific to their patient population. The result of our pain-specific study is comparable with a large, recent study on misdiagnosis in MUS, in which unexplained pain formed a subgroup.[3] Two other studies on MUS in general also show similar results,[12,13] but these do not separately report on patients with pain.

We did not find any significant baseline predictors of misdiagnosis in our study. However, this analysis was underpowered because of the small number of new diagnoses. Thus, no definite conclusions can be drawn about predictive factors.

Since CUP is a heterogeneous clinical problem, we collected our patients from different medical centers and from different outpatient clinics to increase generalizability of our results. To this same end, we used a descriptive and reproducible definition of CUP. At follow-up we asked patients to report a new medical condition. The evaluation of medical records ensured that we would not make false assumptions about whether or not a newly reported diagnosis was a plausible cause for the pain at inclusion. The issue of plausibility, however, can also be regarded as a limitation, because the medical records were interpreted by the study team and because the medical records are not always clear or complete with regard to new diagnoses. Other limitations of our study are the proportion of non-response at follow-up (35%), and the possibility that new diagnoses were underreported by responders.

In conclusion, in patients who were initially diagnosed as having chronic, unexplained pain, we found a low rate (1.6%) of new diagnoses that could explain the pain symptoms during 16-month follow-up. This rate of misdiagnosis is similar to that reported by others for medically unexplained symptoms in general. This finding suggests that physicians can be fairly confident in labeling chronic pain symptoms as unexplained. However, as always in medicine, certainty is not guaranteed, as is shown by the 4 cases of misdiagnosis in this study. A diagnostic mind-set remains indispensable for physicians who are consulted by a patient with pain that appears to be medically unexplained.

REFERENCES

1. Nimnuan C, Hotopf M, Wessely S. Medically unexplained symptoms: an epidemiological study in seven specialities. J Psychosom Res 2001;51:361-7.
2. Aggarwal VR, McBeth J, Zakrzewska JM, et al. The epidemiology of chronic syndromes that are frequently unexplained: do they have common associated factors? Int J Epidemiol 2006;35:468-76.
3. Stone J, Carson A, Duncan R, et al. Symptoms 'unexplained by organic disease' in 1144 new neurology out-patients: how often does the diagnosis change at follow-up? Brain 2009;132:2878-88.
4. Snijders TJ, de Leeuw FE, Klumpers UM, et al. Prevalence and predictors of unexplained neurological symptoms in an academic neurology outpatient clinic--an observational study. J Neurol 2004;251:66-71.
5. Carson AJ, Stone J, Warlow C, et al. Patients whom neurologists find difficult to help. J Neurol Neurosurg Psychiatry 2004;75:1776-8.
6. Slater ET, Glithero E. A follow-up of patients diagnosed as suffering from "hysteria". J Psychosom Res 1965;9:9-13.

7. Stone J, Smyth R, Carson A, et al. Systematic review of misdiagnosis of conversion symptoms and "hysteria". BMJ 2005;331:989. [8] Mayer EA, Bushnell MC. Functional Pain Syndromes: Presentation and Pathophysiology. Seattle, WA: IASP press 2009.

9. Spinhoven P, Ormel J, Sloekers PP, et al. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997;27:363-70.

10. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.

11. Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? Lancet 1999;354:936-9.

12. Carson AJ, Best S, Postma K, et al. The outcome of neurology outpatients with medically unexplained symptoms: a prospective cohort study. J Neurol Neurosurg Psychiatry 2003;74:897-900.

13. Crimlisk HL, Bhatia K, Cope H, et al. Slater revisited: 6 year follow up study of patients with medically unexplained motor symptoms. BMJ 1998;316:582-6.

4

Determinants of pain intensity and quality of life in chronic, unexplained pain

Tom J. Snijders
Albert J.M. van Wijck
K. Seng Liem
Johannes W.G. Jacobs
Laurien L. Teunissen
A.L. Liem
Frank Koerselman
Dieuwke S. Veldhuijzen
Jan van Gijn

Submitted for publication

ABSTRACT

Background: Chronic, unexplained pain (CUP) is a common, heterogeneous clinical problem. Previous research suggests that several CUP syndromes (also known as functional pain syndromes) have many clinical and pathophysiological characteristics in common and form a clinical spectrum rather than constituting separate entities.

Methods: To find determinants for current pain intensity and health-related quality of life (HRQOL), we performed a cross-sectional study among 422 patients from outpatient clinics of different medical specialties who had been diagnosed with a CUP syndrome.

Results: Independent determinants for high current pain intensity were high degrees of somatization, catastrophizing and a dysfunctional coping style. The often-reported influences of age, gender and duration of pain symptoms on pain severity could not be reproduced. We found an association of both widespread pain and anxiety/depression with pain severity in univariable analysis, but these associations did not remain significant in multivariable analysis. Involvement in pain-related medicolegal conflicts, high degrees of somatization, catastrophizing, a dysfunctional coping style, male gender and high current pain intensity were determinants for low physical HRQOL. Independent determinants for poor mental HRQOL were male gender, high degrees of anxiety and depression, and – only to a marginal extent – current pain intensity.

Conclusions: We identified several psychological and physical risk factors for pain intensity and quality of life in a clinically heterogeneous population of CUP patients. This study does not confirm the role of widespread pain symptoms, anxiety and depression, age, gender and pain duration as independent determinants of pain severity in CUP.

INTRODUCTION

In many patients with chronic pain no straightforward medical cause for their pain can be found on clinical evaluation. This group of chronic, unexplained pain (CUP) patients includes patients with so-called 'functional pain syndromes',[1] such as fibromyalgia and non-specific low back pain. Estimations of the population prevalence in CUP range from 2 to 40%,[2] while CUP is diagnosed in one-third of referrals to hospital outpatient clinics.[3,4] CUP patients are characterized by low health-related quality of life (HRQOL),[5] high health care utilization,[6] and decreased participation in everyday life activities.

Despite the obvious heterogeneity within the CUP spectrum, e.g. in pain location, it has been argued that the different CUP syndromes are part of a clinical spectrum rather than being distinct pathophysiological entities.[7] This view is supported by studies that demonstrate overlap in symptom profiles,[8] psychological states (anxiety, depression and dysfunctional coping),[9,10] and in pathophysiological mechanisms, specifically amplification of pain signals in the central nervous system.[11,12] Studying the group of CUP patients as a whole may prove helpful in unraveling the impact of each of the biological, psychological and social factors involved in CUP.

Pain has a severe impact on HRQOL in pain disorders with a known cause, such as neuropathic pain,[13] and possibly even more in CUP syndromes.[14] Interestingly, in a study that predominantly involved musculoskeletal and non-specific pain symptoms, pain catastrophizing was a better predictor of HRQOL than pain intensity itself.[5] Further evidence that, in CUP, the relationship between pain intensity and HRQOL is not straightforward, would be important in defining meaningful outcome measures for research and clinical practice.

Expansion of knowledge on determinants of pain and HRQOL in CUP is needed for proper patient counseling, for selection of treatment, and for patient stratification in therapeutic research. Prospectively collected data on the relation between putative risk factors and pain severity, HRQOL, and prognosis in CUP are scarce, since previous epidemiological studies have focused either on subgroups of CUP, such as low back pain,[15] or on chronic pain in general.[16] Also, many studies studied only one or a few potential determinants.[17]

In this paper, we present data on a large CUP cohort, in whom we assessed a wide range of factors that have previously been implicated in the initiation and maintenance of CUP. We aimed to (1) determine the independent association of several determinants with pain severity and HRQOL; and (2) study the relation between pain and HRQOL and the interaction with other determinants. On the basis of earlier studies, we hypothesized that the relationship between pain and HRQOL would be modified by coping strategy.

MATERIALS AND METHODS

In this paper, we present a cross-sectional analysis of baseline data that were collected as part of a prospective cohort study. The study was approved by the local medical ethics committee in accordance with the Declaration of Helsinki (2008).

Patients

At the University Medical Center Utrecht, the Netherlands (U), a university hospital, and the St Antonius Hospital in Utrecht and Nieuwegein, the Netherlands (A), a large non-university hospital, we consecutively screened newly referred patients from the outpatient clinics of the departments of Neurology (U and A), Pain Medicine (U and A) and Rheumatology (U only) for eligibility. We screened the referral letters beforehand if possible, and checked patient records for eligibility after the consultation in all cases.

Inclusion criteria were:

- Adult patients (18 years or older) with pain lasting at least three months.
- No conventional medical cause could be determined on routine medical evaluation. Routine medical evaluation consisted of history taking, physical examination, and review of previous medical history by the treating physician. Ancillary investigations were performed at the treating physician's discretion, in accordance with professional standards and (inter-)national guidelines; no extra ancillary studies were performed for the purpose of this study.
- A diagnosis of a specific functional pain syndrome, e.g. fibromyalgia or temporomandibular joint dysfunction, was allowed, since these diagnoses are part of the spectrum of CUP. However, such a diagnosis was not necessary for inclusion. Patients who met the Dutch criteria for non-specific low back pain were also enrolled;[18] this group included patients with pain at or near the sacro-iliac joint(s) or the facet joints. Mild degenerative changes on imaging studies of the low back did not lead to exclusion, since such imaging findings correlate poorly with clinical symptoms.[19] Further information on in- and excluded pain syndromes is given in supplementary table S4.1.
- Sufficient knowledge of the Dutch language.

Eligibility was evaluated by the treating physician and reviewed by the study team. Discussions about eligibility were solved in team meetings by consensus. Only after permission from the treating physician had been obtained did one of the study team members proceed to further inform the patient about the study, either at the outpatient clinic or by telephone, and to

ask the patient to participate. The patients then received further written information and the questionnaires. Non-responders received up to two reminders, by telephone or by mail.

Data collection and questionnaires

From medical records, we collected data on age, gender, current pain diagnosis and previous pain diagnoses. Information on the diagnosis of current and previous functional pain syndromes was not available for all patients, since not all physicians involved routinely use the same diagnostic labels.

Patients completed the following questionnaires (the scores or other outcome measures derived from these questionnaires are given after the colon following each instrument):

1. The McGill Pain questionnaire, Dutch language version (MPQ-DLV): pain location (drawings on pain mannequins) – we classified a patient's symptoms as 'chronic widespread pain (CWP)' according to criteria of the American College of Rheumatology;[20] pain duration; visual analogue scale (VAS) ratings for current pain intensity as well as mildest and worst pain, with a range from 0 ("no pain at all") to 100 mm ("unbearable pain").[21,22]
2. The Multidimensional Pain Inventory, Dutch language version (MPI-DLV):[23] we calculated the coping profile with available standard scoring software, on the basis of previously published factorial analysis. This resulted in a Dysfunctional, Interpersonally Distressed, Average, Adaptive Coper or Anomalous subtype (or 'profile').[24]
3. Pain Catastrophizing Scale, Dutch Version (PCS):[25] we calculated the total score for pain catastrophizing.
4. Hospital Anxiety and Depression Scale (HADS), Dutch version:[26,27] the total HADS score was calculated as a compound measure for anxiety and depression; a score above 14 is considered abnormal.
5. Symptoms Check List-90, somatization subscale (SCL-90-SOM),[28] Dutch version (Swets & Zeitlinger b.v., Lisse, Netherlands): we calculated the total SCL-90-SOM score as a measure of the tendency for somatization. The SCL-90-SOM measures somatic symptoms and is commonly used as a measure for somatization, although scores may also be elevated due to somatic symptoms related to physical illness.[29]
6. A self-designed questionnaire contained items on current and previous treatment for pain symptoms (categorized as (a) medication, (b) physical

therapy, (c) invasive procedures or transcutaneous electrical nerve stimulation (TENS), or (d) multidisciplinary pain management program); current or past involvement in a medicolegal procedure for (financial) compensation in relation to pain; work status, including sick leave and disability compensation.

7. The Short Form-36 health questionnaire, Dutch Version:[30] The Mental and Physical Component Summary (SF-MCS and SF-PCS) scores served as measures for HRQOL. For analysis, the SF-MCS and SF-PCS scores were standardized by means of Dutch reference data.[31]

For each of the scales and questionnaires, we only calculated the total or compound score if a minimum number of items (as stated in the different validation studies) was completed.

Statistical analysis

Data were entered and analyzed in SPSS version 15.0.1. A total of 9 determinants were extracted from the questionnaire data (table 4.3). Questionnaire data were treated as continuous data (rather than the categorization or dichotomization of scores according to published cut-off scores),[32] except for MPI data, which we categorized into the different coping profiles. Current pain intensity (VAS score) and HRQOL (SF-MCS and SF-PCS score) served as outcome measures.

In total, 5.5% of all data (single questionnaire items and sum scores combined) were missing. Missing values for all determinants and outcome measures were imputed by means of single putation before final analysis was performed. Imputation of missing values has been shown to produce unbiased results in incomplete datasets, whereas other methods to handle missing data introduce bias, especially in the context when missing items are not missing completely at random.[33]

We first studied the relationship of each single determinant with current pain as well as the relationship of each determinant with physical and mental HRQOL (univariable analysis). We used non-parametric tests for the dichotomous determinants (Mann-Whitney test) and for other categorical determinants (Kruskal-Wallis test), since we found significant deviations from normality for these tests of association (Kolmogorov-Smirnov test, $p<0.05$). For continuous determinants, we performed simple linear regression; linear regression provided a better fit than more complex or non-parametric models.

To study whether the determinants of interest are independently associated with current pain intensity and HRQOL (and not merely associated with the outcome measure due to confounding) we then performed multiple regression analysis for each of the three outcome measures: we entered all determinants in a linear regression model for current pain and for physical and mental HRQOL. We checked the data for collinearity and found no relevant

collinearity, so all determinants could be included in the model. Categorical determinants were transformed into multiple dichotomous variables, one for each category. As we considered the relationship between current pain intensity and HRQOL as hierarchic, wherein pain is a potential determinant of HRQOL, we calculated two separate models for HRQOL: one including current pain as a determinant, and one without current pain.

To study the relation between current pain intensity and HRQOL, we performed regression modeling with HRQOL scores as outcome measures and the same determinants as before including current pain intensity; to this model we added interaction terms for the interaction between pain and the other determinants.

RESULTS

Patient inclusion

The flowchart of patient inclusion (figure 4.1) shows that 748 patients were eligible during the study period, of which 326 (44%) could not be included, mostly due to non-response (32%).

Most patients came from the department of Neurology (63%), followed by Pain medicine (21%) and Rheumatology (16%). Patients were evenly distributed between the academic hospital (53%) and the general hospital (47%). In our multivariable analysis, we did not find an independent association between the hospital or outpatient clinic and our outcome measures (pain and physical and mental HRQOL).

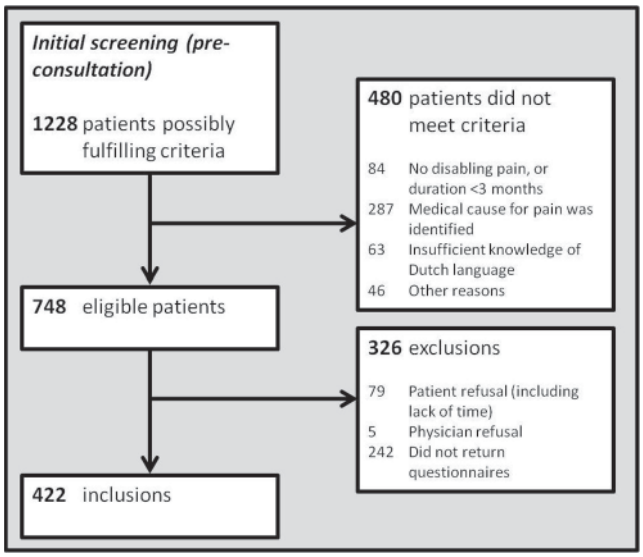

Figure 4.1 Flowchart of in- and exclusions in this study.

Patient characteristics

Patient characteristics are presented in table 4.1. In line with most chronic pain conditions, most patients (69%) were female. Pain symptoms were present for a median of 4 years (interquartile range: 1.5 – 10 years). A substantial number of patients were involved in medicolegal conflicts (18%) and/or received financial compensation (22%) in relation to their pain symptoms. Most patients (81%) used analgesic medication and underwent (current or previous) physical therapy (87%). HADS scores were generally high, and exceeded the threshold (of 14) for anxiety and depression in 41%. Figure 4.2 shows the distribution of current pain scores.

Determinants of current pain intensity

The univariable analysis (supplementary table S4.2) indicated that the presence of chronic widespread pain, high SCL-90-SOM-scores for somatization, high catastrophizing scores (PCS), and a high degree of anxiety and depression (HADS) were associated with high current pain intensity (VAS score). Coping style as determined from the MPI was also associated with current pain intensity; post-hoc tests showed that pain scores were highest for the 'Dysfunctional' profile, followed by 'Interpersonally distressed' and 'Average', and lowest for the 'Adaptive' and 'Anomalous' profiles. Gender, age, duration of symptoms and previous or current legal procedures were not associated with current pain intensity.

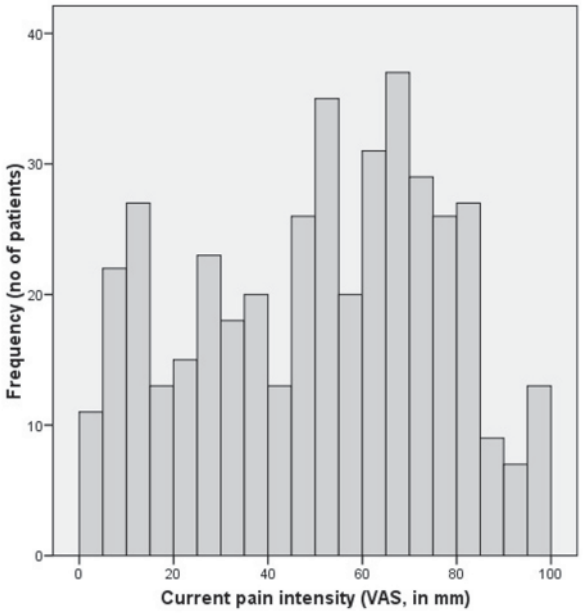

Figure 4.2 Distribution histogram of current pain intensity as measured by visual analogue scale (VAS).

Table 4.1 Patient characteristics. Data presented are number of patients, with percentage of total between brackets, unless specified otherwise.

Demographic variables	
Females	289 (68.5%)
Age in years (mean ± SD)	49.9 ± 14.6
Pain duration in months (median (IQR))	48 (18.75 – 120)
Widespread pain	122 (28.9%)
On sick leave or disability compensation in relation to pain	90 (21.3%)
Involvement in a legal conflict/procedure in relation to pain	76 (18.0%)
Current procedure	36 (8.5%)
Past procedure	40 (9.5%)
Current and previous therapy	
Physical	365 (86.5%)
Invasive and TENS	209 (49.5%)
Multidisciplinary/rehabilitation	47 (11.1%)
Medication	343 (81.3%)
Paracetamol/NSAIDs	318 (75.4%)
Antineuropathic drugs	57 (13.5%)
Opioids	133 (31.5%)
Questionnaires	
Hospital Anxiety and Depression Scale (HADS) score (median (IQR))	12.5 (8 – 18)
Pain Catastrophizing Scale (PCS) score (median (IQR))	20 (12 – 30.3)
Symptom Check List, somatization subscale (SCL-90-SOM) (median (IQR))	26 (21 – 33)
Multidimensional Pain Inventory (MPI), coping profile[a]	
Anomalous	21 (5.0%)
Adaptive coper	53 (12.6%)
Average	110 (26.1%)
Interpersonally distressed	65 (15.4%)
Dysfunctional	104 (24.6%)
Missing (insufficient MPI data for calculation)	69 (16.4%)
Outcome measures	
Current pain, Visual Analogue Scale in mm (median (IQR))	52.3 (28.8 – 70.0)
Short Form 36 Physical Component Subscale (SF-PCS) score (median (IQR))	33.8 (27.9 – 40.1)
Short Form 36 Mental Component Subscale (SF-MCS) score (median (IQR))	46.6 (38.4 – 52.8)

[a] Data before imputation.
IQR = interquartile range; NSAIDs = non-steroid anti-inflammatory drugs; SD = standard deviation; TENS = transcutaneous electrical nerve stimulation.

In multiple regression analysis (table 4.2), high SCL-90-SOM-scores for somatization, high catastrophizing scores on the PCS, and a 'Dysfunctional' coping style were all independently associated with high current pain intensity. A past legal procedure was also independently associated with high current pain intensity, but a current legal procedure was not. The 'Anomalous' coping style was found to be an independent determinant for low current pain intensity.

The other determinants were not independently associated with current pain intensity. In particular, the significant associations of current pain intensity with widespread pain and with anxiety and depression (HADS) from the univariable analyses did not hold up in the multiple regression analysis. In the multiple regression model, the proportion of the variance in current pain intensity that could be explained by all determinants (adjusted R^2) was 21.7%.

Determinants of health-related quality of life

The univariable analyses (supplementary table S4.3) showed that widespread pain, a past or current legal procedure, high current pain intensity, long duration of symptoms, high anxiety/depression scores, and a high degree of catastrophizing and somatization were all associated with low physical HRQOL (SF-PCS-scores).

Table 4.2 Determinants of current pain intensity: multiple regression analysis

Determinant	β-value (95%-CI)	p-value
Gender	1.799 (-3.153 – 6.751)	0.476
Age (y)	-0.041 (-0.205 – 0.123)	0.620
Pain duration (months)	0.002 (-0.018 – 0.021)	0.854
Chronic widespread pain	2.340 (-2.994 – 7.673)	0.389
Coping profile/MPI cluster		
Anomalous	-17.380 (-26.828 – -7.932)	< 0.001
Adaptive coper	-4.169 (-11.026 – 2.689)	0.233
Average	Reference group	
Interpersonally distressed	0.775 (-5.827 – 7.377)	0.818
Dysfunctional	7.023 (0.851 – 13.195)	0.026
Legal procedure		
Previous	8.534 (0.748 – 16.320)	0.032
Current	3.287 (-4.897 – 11.471)	0.430
Anxiety & depression (HADS)	0.044 (-0.355 – 0.444)	0.827
Pain catastrophizing (PCS)	0.562 (0.336 – 0.789)	< 0.001
Somatization (SCL-90-SOM)	0.517 (0.205 – 0.828)	0.001

CI = confidence interval. For abbreviations of questionnaires: see table 4.1.

Coping profile from the MPI was also associated with physical HRQOL, with post-hoc tests showing lower physical HRQOL for the 'Dysfunctional', 'Interpersonally distressed' and 'Average' profiles than for the 'Adaptive' and 'Anomalous' profiles.

The multiple regression analysis (table 4.3) yielded the following determinants for low physical HRQOL (SF-PCS-scores): male gender, presence of widespread pain, a past or current legal procedure, high degree of somatization, and high current pain intensity. An 'Adaptive' or 'Anomalous' coping style was independently associated with high physical HRQOL (compared to the reference group 'Dysfunctional'). High anxiety and depression scores were associated with high physical HRQOL.

We repeated the multiple regression analysis for physical HRQOL with a model that did not include current pain; the same determinants were again found, as well as a significant influence of catastrophizing and an 'Interpersonally distressed' coping profile (higher physical HRQOL than the reference group 'Dysfunctional', data not shown). The proportion of the variance in physical HRQOL that could be explained by all determinants (adjusted R^2) was 28% in the model that did not include current pain intensity and 34% in the model with current pain intensity.

Table 4.3 Determinants of health-related quality of life (HRQOL): multiple regression analysis

Determinant	Physical HRQOL (SF-PCS)		Mental HRQOL (SF-MCS)	
	β-value (95%-CI)	p-value	β-value (95%-CI)	p-value
Gender	2.128 (0.599 – 3.657)	0.007	4.415 (2.853 - 5.977)	< 0.001
Age (y)	-0.042 (-0.093 – 0.009)	0.103	0.025 (-0.026 - 0.076)	0.346
Pain duration (months)	-0.004 (-0.010 – 0.002)	0.223	0.001 (-0.005 - 0.007)	0.658
Chronic widespread pain	-4.169 (-5.815 – -2.523)	< 0.001	1.111 (-0.573 - 2.795)	0.196
Coping profile/MPI cluster				
Anomalous	3.953 (0.878 – 7.028)	0.012	-0.713 (-3.857 - 2.431)	0.657
Adaptive coper	3.778 (1.532 – 6.024)	0.001	0.681 (-1.614 - 2.976)	0.561
Average	0.301 (-1.614 – 2.216)	0.758	0.581 (-1.377 - 2.539)	0.561
Interpersonally distressed	1.844 (-0.208 – 3.896)	0.079	-0.016 (-2.113 - 2.081)	0.988
Dysfunctional	Reference group		Reference group	
Legal procedure				
Previous	-2.917 (-5.332 – -0.502)	0.018	0.897 (-1.573 - 3.367)	0.477
Current	-4.303 (-6.829 – -1.777)	0.001	1.902 (-0.681 - 4.485)	0.150
Anxiety & depression (HADS)	0.167 (0.044 – 0.290)	0.008	-0.929 (-1.054 - -0.804)	< 0.001
Pain catastrophizing (PCS)	-0.061 (-0.134 – 0.012)	0.097	-0.070 (-0.144 - 0.004)	0.065
Somatization (SCL-90-SOM)	-0.220 (-0.318 – -0.122)	< 0.001	-0.034 (-0.134 - 0.066)	0.501
Current pain intensity (VAS)	-0.098 (-0.127 – -0.069)	< 0.001	0.034 (0.003 - 0.065)	0.029

CI = confidence interval; For abbreviations of questionnaires: see table 4.1.

To further explore the relationship between anxiety and depression and physical HRQOL, we repeated the multiple regression model for physical HRQOL (including current pain) with addition of interaction terms between total HADS score and the other determinants. In this interaction analysis, a significant interaction between total HADS score and an 'Adaptive' coping profile was found ($F(1;421)=4.89$, $p=0.028$). Repeating the univariable analysis (simple linear regression) of the relationship between total HADS score and physical HRQOL separately for 'Adaptive copers' and other patients showed that HADS score and physical HRQOL are inversely related in 'Adaptive copers' (B=- 0.597; standard error (SE)=0.185; p=0.002), but not in patients with other coping profiles (B=-0.086; SE=0.062; p=0.166).

We found the following determinants for low mental HRQOL (SF-MCS-scores) in univariable analysis (supplementary table S4.3): male gender, high current pain intensity, and high degrees of catastrophizing, anxiety and depression, and somatization. Coping style was also associated with mental HRQOL; post-hoc tests revealed lowest mental HRQOL for the 'Dysfunctional', 'Interpersonally distressed' and 'Anomalous' profiles, intermediate mental HRQOL for the 'Average' profile, and the highest for the 'Adaptive' profile.

In multiple regression analysis, determinants for lower mental HRQOL were male gender and high anxiety and depression scores, with a trend for catastrophizing (p=0.065). High current pain intensity was associated with high mental HRQOL. Repeating multiple regression analysis for mental HRQOL without current pain as a determinant revealed similar results, but the trend for catastrophizing was no longer found. The proportion of the variance in mental HRQOL that could be explained by all determinants (adjusted R^2) was 50%, both for the model that did not include current pain intensity and the model with current pain intensity.

Modifying factors in the relationship between pain and HRQOL

Current pain intensity was significantly and negatively correlated with physical HRQOL (Pearson's $r=-0.430$; $p<0.001$; figure 4.3A). In multivariable analysis, a high level of current pain intensity was a strong independent determinant of low physical HRQOL (table 4.3).

In contrast, current pain intensity was only marginally negatively correlated with mental HRQOL (Pearson's $r=-0.106$; $p=0.03$; figure 4.3B). In multiple regression analysis, the direction of this relationship was inverted: high current pain intensity was an independent determinant of high mental HRQOL (table 4.3).

We repeated the multiple regression analysis for determinants of physical and mental HRQOL with addition of interaction terms between current pain intensity and other determinants (i.e. current pain x coping profile from MPI; current pain x catastrophizing; etc). We did not find any significant interactions between pain and coping profiles. In the interaction analysis for determinants of *physical* HRQOL, we failed to detect any significant interactions between pain

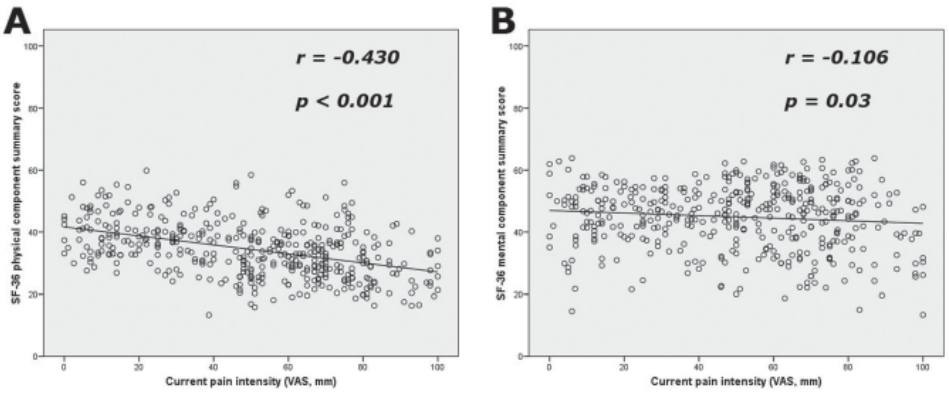

Figure 4.3 Scatterplots of the relationship between current pain intensity (visual analogue scale (VAS) score) and health-related quality of life (SF-36 score). (A) Relationship between current pain intensity and physical component score of SF-36. (B) Relationship between current pain intensity and mental component score of SF-36.

and coping profiles, but we did find a significant interaction between current pain and current or previous involvement in a legal conflict (F=3.40; p=0.034): in patients involved in a current legal conflict, the negative relationship between current pain intensity and physical HRQOL was less strong than in patients not involved in a current legal conflict. In the interaction analysis for determinants of *mental* HRQOL, we found no significant interactions between current pain on the one hand, and coping profile or other determinants on the other.

DISCUSSION

In this multidisciplinary, cross-sectional study on a prospectively collected cohort of patients with chronic, unexplained pain, we assessed the relationship between several potentially important clinical and psychological factors on the one hand, and pain intensity and health-related quality of life (HRQOL) on the other. Our main findings are:

1. Widespread pain, somatization, pain catastrophizing, anxiety/depression and coping profile are associated with current pain intensity in univariable analyses; other factors such as gender and duration of pain symptoms were not. Multiple regression analysis showed that only somatization, catastrophizing, and an 'Anomalous' or 'Dysfunctional' coping profile were independently associated with current pain intensity, suggesting that the influence of widespread pain and of anxiety/depression on current pain is better

explained by other factors such as somatization, catastrophizing or coping profile. Overall, the determinants we studied account for only a limited proportion of the variance in current pain intensity.

2. The following determinants are independently associated with physical HRQOL: gender, widespread pain, (an 'Anomalous' or 'Adaptive' *versus* a 'Dysfunctional') coping style, current or past involvement in legal conflicts related to pain, anxiety/depression, somatization, and current pain intensity. High anxiety and depression scores are associated with low physical HRQOL on univariable analysis, but this – surprisingly – converts to a positive association on multiple regression analysis, possibly through a modifying effect of coping style. Pain duration and catastrophizing are univariably, but not independently, associated with physical HRQOL.
3. Gender, anxiety/depression, and current pain intensity are independently associated with mental HRQOL. We found, unexpectedly, that high current pain intensity is independently associated with good mental HRQOL. Pain catastrophizing and somatization are univariably, but not independently, associated with mental HRQOL.
4. Severe current pain is associated with poor physical HRQOL. This relationship was not significantly modified by coping profile, but we did find an interaction between pain and the existence of current legal conflicts in the model for physical HRQOL. The analysis on the relationship between current pain and mental HRQOL yielded contradictory results and small effect sizes, which suggests that mental HRQOL in CUP is not strongly determined by pain intensity.

Several studies have reported on associations between clinical and psychosocial determinants on one hand, and the existence and outcome of chronic pain and HRQOL on the other (reviewed in[34]). Previously reported sociodemographic determinants for development and persistence of chronic pain include female gender and old age, as well as occupational and other sociocultural factors.[34] The psychological factors most solidly associated with chronic pain are depression, somatization, catastrophizing, and coping profile.[35-39] By comparison, in our cohort of CUP patients, psychological variables are the most important determinants of current pain intensity; the previously reported relationship between pain intensity and factors such as age, gender, and pain duration was not confirmed.[34] Current pain intensity, in turn, is a strong determinant of physical HRQOL. Physical HRQOL is associated with a broad range of demographic, pain-related, and psychological factors, whereas determinants of mental HRQOL are less numerous.

In multiple regression analysis, we found that the investigated determinants account for only a limited proportion of the variation in current pain intensity (22%) and physical (22-34%) and mental (50%) HRQOL. It cannot be deduced from our data what source of the remaining variation there may be. It is likely that certain treatments play a role, but we cannot reliably

study their effects in our cross-sectional design since we were not informed about the treating physician's reason for choosing a certain treatment; therefore, analysis of treatment effects would probably be biased due to confounding by indication. In addition to treatment, cultural background and other sociodemographic factors may be important.[34] It is also possible that intrinsic differences between individuals in pain sensitivity and somatosensory processing affect pain intensity, which might be measured with neurophysiologic methods or quantitative sensory testing.[11]

Although the cross-sectional nature of our data precludes conclusions on causality of the associations, the comparison of univariable analyses and multiple regression still offers interesting insights.

- In univariable analysis, patients with widespread pain have more severe pain than for more localized pain symptoms, but this effect seems to be mediated by psychological factors such as somatization, catastrophizing and coping profile. This may mean that the existence of widespread pain symptoms, when compared with more localized CUP symptoms, is a marker of CUP severity through a worse (psychological) risk factor profile, rather than being an independent factor. This adds to the hypothesis that widespread pain syndromes such as fibromyalgia are (the most severely affected) part of a clinical spectrum of chronic pain syndromes rather than a separate disease entity.[40]
- The association between anxiety/depression and pain intensity seems to be better explained by other psychological factors such as somatization, catastrophizing and coping profile. In contrast, previous studies found that anxiety and depression form an independent determinant of low back pain and other chronic pain states.[39] The differences between previous studies and our data may be due to the fact that previous studies did correct for all the factors we studied in multivariable analysis. Also, differences in baseline characteristics and the use of more narrowly defined (e.g. syndrome-based) inclusion criteria in previous studies may be the cause. A possible explanation for the lack of an independent association between anxiety/depression and pain severity in our data is that anxiety and depression are not the cause, but rather the consequence of CUP.[41] Alternatively, both chronic pain and anxiety/depression may be the consequence of other factors.
- Pain catastrophizing is an independent determinant of pain intensity, but not of physical and mental HRQOL. The effect of pain catastrophizing on HRQOL that we found in univariable analysis thus seems to be mediated by other factors, possibly by pain severity itself.

- Involvement in a legal claim has previously been implied as a negative prognostic factor in chronic pain, as well as a predictor of poor treatment outcome.[17] Although we did not find a direct association of legal procedures with current pain or HRQOL, we did find that a (current) legal procedure blurs the relationship between pain severity and physical HRQOL in CUP; this may mean that, in the context of an ongoing legal procedure, clinicians should not presume that treatments aimed at pain relief will also automatically lead to a better quality of life.

CUP is a heterogeneous clinical problem, but converging lines of evidence support the notion that CUP should be studied as a continuous spectrum rather than as a collection of separate syndromes.[1,7] We adopted a broad, descriptive and reproducible definition of CUP and prospectively collected our patients from multiple centers and medical disciplines, so that our findings may be extrapolated to CUP as a whole as well as to any of the sub-syndromes.

The cross-sectional nature of this study forms its most important limitation. Although the multiple regression analysis with a large number of determinants minimizes the risk that our findings are the consequence of confounding effects, it is still uncertain whether the associations we found represent causal relationships. Importantly, it is not possible to determine the effect of (previous or current) treatments on current pain and HRQOL in this design.

In conclusion, we identified a number of determinants of pain intensity (somatization, catastrophizing and coping profile) and many determinants of health-related quality of life (HRQOL) within the heterogeneous population of chronic, unexplained pain patients. We could not confirm the often-reported association of pain intensity with a widespread pattern of pain, anxiety and depression, age, gender and pain duration. Pain intensity itself was a strong determinant of physical, but not of mental aspects of HRQOL. The limited proportion of explained variance for pain intensity and HRQOL in our analyses indicates that the currently known risk factors cannot fully explain the variation in clinical severity of CUP.

In CUP, no diagnosis in the classical etiological sense is available. The findings from the current study may form a starting point for the identification of subsets of patients – based on the relevant determinants – who will respond to specific treatment strategies, targeted at the underlying factors rather than on what is common practice for the syndrome-based diagnosis in question. In order to classify an individual patient for therapeutic purposes, and in order to better explain the variation in CUP severity, descriptive data such as those in the present study should be combined with identification and measurement of biomarkers or endophenotypes such as quantitative sensory testing and neuroimaging, ideally in combination with the genetic profile, in order to classify pain patients and their symptoms at a mechanistic level.[34] Such datasets should longitudinally be related to outcome and response to existing treatments.

ACKNOWLEDGEMENTS

The authors wish to thank H.B. Brouwers, M.D., A.C. Baakman, M.D., S.T. Idzinga, M.D., M.J. Overdijk, M.D., H.C.H.P. Broekman and F. Smits, M.D., for assistance in patient acquisition and data entry; the physicians at the five participating outpatient clinics for their support in inclusion of patients; prof. K.G. Moons for valuable advice on study design.

REFERENCES

1. Mayer EA, Bushnell MC. Functional Pain Syndromes: Presentation and Pathophysiology. Seattle, WA: IASP press; 2009.
2. Kerssens JJ, Verhaak PF, Bartelds AI, Sorbi MJ, Bensing JM. Unexplained severe chronic pain in general practice. Eur J Pain 2002;6:203-12.
3. Maiden NL, Hurst NP, Lochhead A, Carson AJ, Sharpe M. Medically unexplained symptoms in patients referred to a specialist rheumatology service: prevalence and associations. Rheumatology 2003;42:108-12.
4. Snijders TJ, de Leeuw FE, Klumpers UMH, Kappelle LJ, van Gijn J. Prevalence and predictors of unexplained neurological symptoms in an academic neurology outpatient clinic - An observational study. J Neurol 2004;251:66-71.
5. Lame IE, Peters ML, Vlaeyen JW, Kleef M, Patijn J. Quality of life in chronic pain is more associated with beliefs about pain, than with pain intensity. Eur J Pain 2005;9:15-24.
6. Smith GR, Jr., Monson RA, Ray DC. Patients with multiple unexplained symptoms. Their characteristics, functional health, and health care utilization. Arch Intern Med 1986;146:69-72.
7. Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? Lancet 1999;354:936-9.
8. Aaron LA, Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. Ann Intern Med 2001;134:868-81.
9. Koleck M, Mazaux JM, Rascle N, Bruchon-Schweitzer M. Psycho-social factors and coping strategies as predictors of chronic evolution and quality of life in patients with low back pain: a prospective study. Eur J Pain 2006;10:1-11.
10. Petrak F, Hardt J, Kappis B, Nickel R, Egle UT. Determinants of health-related quality of life in patients with persistent somatoform pain disorder. European Journal of Pain 2003;7:463-71.
11. Pfau DB, Rolke R, Nickel R, Treede RD, Daublaender M. Somatosensory profiles in subgroups of patients with myogenic temporomandibular disorders and Fibromyalgia Syndrome. Pain 2009;147:72-83.
12. Snijders TJ, Ramsey NF, Koerselman F, van Gijn J. Attentional modulation fails to attenuate the subjective pain experience in chronic, unexplained pain. Eur J Pain 2010;14:282-10.
13. Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: review and implications. Neurology 2007;68:1178-82.

14. Veldhuijzen DS, Greenspan JD, Smith MT. Sleep and quality of life in chronic pain. In: Verster JC, Pandi-Perumal SR, Streiner DL, editors. Sleep and quality of life in clinical medicine.Totowa, NJ: Humana Press; 2008. p. 187-98.

15. Von Korff M, Deyo RA, Cherkin D, Barlow W. Back pain in primary care. Outcomes at 1 year. Spine 1993;18:855-62.

16. Tripp DA, VanDenKerkhof EG, McAlister M. Prevalence and determinants of pain and pain-related disability in urban and rural settings in southeastern Ontario. Pain Res Manag 2006;11:225-33.

17. Rasmussen C, Leboeuf-Yde C, Hestbaek L, Manniche C. Poor outcome in patients with spine-related leg or arm pain who are involved in compensation claims: a prospective study of patients in the secondary care sector. Scand J Rheumatol 2008;37:462-8.

18. Koes BW, Sanders RJ, Tuut MK. [The Dutch Institute for Health Care Improvement (CBO) guideline for the diagnosis and treatment of aspecific acute and chronic low back complaints]. Ned Tijdschr Geneeskd 2004;148:310-4.

19. van Tulder MW, Assendelft WJ, Koes BW, Bouter LM. Spinal radiographic findings and nonspecific low back pain. A systematic review of observational studies. Spine (Phila Pa 1976) 1997;22:427-34.

20. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160-72.

21. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1:277-99.

22. Verkes RJ, Vanderiet K, Vertommen H, Van der Kloot WA, Van der Meij J. De MPQ-DLV: een standaard nederlandstalige versie van de McGill Pain Questionnaire voor België en Nederland. In: Kloot WA van der, Vertommen H, editors. De MPQ-DLV. Een standaard nederlandstalige versie van de McGill Pain Questionnaire. Achtergronden en inleiding.Lisse: Swets & Zeitlinger BV; 1989. p. 57-74.

23. Lousberg R, Van Breukelen G.J., Groenman NH, Schmidt AJ, Arntz A, Winter FA. Psychometric properties of the Multidimensional Pain Inventory, Dutch language version (MPI-DLV). Behav Res Ther 1999;37:167-82.

24. Turk DC, Rudy TE. Toward an empirically derived taxonomy of chronic pain patients: integration of psychological assessment data. J Consult Clin Psychol 1988;56:233-8.

25. Crombez G, Vlaeyen JW, Heuts PH, Lysens R. Pain-related fear is more disabling than pain itself: evidence on the role of pain-related fear in chronic back pain disability. Pain 1999;80:329-39.

26. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997;27:363-70.

27. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.

28. Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale--preliminary report. Psychopharmacol Bull 1973;9:13-28.

29. Kaplan CP, Miner ME, Mervis L, Newton H, McGregor JM, Goodman JH. Interpretive risks: the use of the Hopkins Symptom Checklist 90-Revised (SCL 90-R) with brain tumour patients. Brain Inj 1998;12:199-205.

30. Ware JE, Jr. SF-36 health survey update. Spine 2000;25:3130-9.

31. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51:1055-68.

32. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med 2006;25:127-41.

33. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006;59:1087-91.

34. Smith BH, Macfarlane GJ, Torrance N. Epidemiology of chronic pain, from the laboratory to the bus stop: time to add understanding of biological mechanisms to the study of risk factors in population-based research? Pain 2007;127:5-10.

35. Dionne CE. Psychological distress confirmed as predictor of long-term back-related functional limitations in primary care settings. J Clin Epidemiol 2005;58:714-8.

36. Dionne CE, Koepsell TD, Von KM, Deyo RA, Barlow WE, Checkoway H. Predicting long-term functional limitations among back pain patients in primary care settings. J Clin Epidemiol 1997;50:31-43.

37. Horng YS, Hwang YH, Wu HC, Liang HW, Mhe YJ, Twu FC, et al. Predicting health-related quality of life in patients with low back pain. Spine 2005;30:551-5.

38. Linton SJ. A review of psychological risk factors in back and neck pain. Spine (Phila Pa 1976) 2000;25:1148-56.

39. Pincus T, Burton AK, Vogel S, Field AP. A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. Spine (Phila Pa 1976) 2002;27:E109-E120.

40. Macfarlane GJ. Generalized pain, fibromyalgia and regional pain: an epidemiological view. Baillieres Best Pract Res Clin Rheumatol 1999;13:403-14.

41. Dersh J, Mayer T, Theodore BR, Polatin P, Gatchel RJ. Do psychiatric disorders first appear preinjury or postinjury in chronic disabling occupational spinal disorders? Spine 2007;32:1045-51.

SUPPLEMENTARY TABLES

Table S4.1 A list of included and excluded pain syndromes in the study. The list primarily contains pain syndromes of which the classification as 'explained' or 'unexplained' may be disputed. Some of the syndromes in the table may overlap in their definitions. The list is not intended to be complete, especially not on the excluded pain syndromes. Consequently, not all patients had a diagnosis from this table; the study team decided on eligibility on an individual basis.

Included pain syndromes	Excluded pain syndromes
• Fibromyalgia • Irritable bowel syndrome • Myofascial pain syndrome • Non-specific low back pain, with or without pseudoradicular radiation of pain • Post-whiplash syndrome or Whiplash associated disorder grade I-II • Psychogenic pain symptoms • Somatoform pain disorder • Temporomandibular joint dysfunction • Tension-type headache	• Complex regional pain syndrome • Failed back surgery syndrome • Headache associated with substance- or medication-(over-)use • Well-defined headache syndromes without a structural cause (for example migraine, cluster headache)

Table S4.2 Determinants of current pain intensity: univariable analysis. The statistical test used is mentioned with each determinant.

Determinant	Categorical determinants		Linear determinants:	
	Median score per category	Test statistic	β-value (95%-CI)	p-value
Gender (female vs male); Mann-Whitney test	54.0 vs 48.0	Z = -1.376		0.169
Age (y); linear regression			-0.121 (-0.292 – 0.050)	0.166
Pain duration (months) ; linear regression			0.008 (-0.013 – 0.028)	0.456
Chronic widespread pain (present vs absent) ; Mann-Whitney test	58.5 vs 50.5	Z = -2.182		0.029
Coping profile/MPI cluster (Anomalous /Adaptive coper/Average/ Interpersonally distressed/ Dysfunctional); Kruskal-Wallis test	17.0 / 37.5 / 52.0 / 52.0 / 64.0	$\chi^2 = 43.795$		< 0.001
Legal procedure (Never / Previous / Current) ; Kruskal-Wallis test	51.5 / 63.0 / 54.5	$\chi^2 = 4.703$		0.095
Anxiety & depression (HADS) ; linear regression			0.983 (0.649 – 1.316)	< 0.001
Pain catastrophizing (PCS) ; linear regression			0.759 (0.563 – 0.956)	< 0.001
Somatization (SCL-90-SOM) ; linear regression			0.955 (0.681 – 1.229)	< 0.001

CI = confidence interval; For abbreviations of questionnaires: see table 4.1.

Table S4.3 Determinants of the physical (SF-PCS) and mental (SF-MCS) component subscales of health-related quality of life: Univariable analysis. The statistical test used is mentioned with each determinant

Determinant	Outcome	Categorical determinants		Linear determinants:	
	SF-scale	Median score per category	Test statistic	β-value (95%-CI)	p-value
Gender (female vs male); *Mann-Whitney test*	SF-PCS	33.7 vs 34.0	Z = -0.616		0.538
	SF-MCS	47.5 vs 43.3	Z = -3.982		< 0.001
Age (y); *linear regression*	SF-PCS			0.000 (-0.058 – 0.058)	0.995
	SF-MCS			0.010 (-0.058 – 0.078)	0.770
Pain duration (months); *linear regression*	SF-PCS			-0.010 (-0.016 – -0.003)	0.007
	SF-MCS			-0.003 (-0.011 – 0.005)	0.430
Chronic widespread pain (present vs absent); *Mann-Whitney test*	SF-PCS	29.5 vs 36.1	Z = -6.355		< 0.001
	SF-MCS	46.8 vs 46.4	Z = -0.237		0.813
Coping profile/MPI cluster (Anomalous/Adaptive coper/ Average/ Interpersonally distressed/Dysfunctional); *Kruskal-Wallis test*	SF-PCS	34.9 / 39.7 / 33.0 / 35.6 / 31.7*	χ^2 = 30.600		< 0.001
	SF-MCS	43.2 / 50.6 / 47.0 / 41.7 / 44.8*	χ = 23.409		< 0.001
Legal procedure (Never/Previous /Current); *Kruskal-Wallis test*	SF-PCS	35.1 / 30.8 / 28.7*	χ = 19.567		< 0.001
	SF-MCS	46.9 / 45.9 / 44.7*	χ = 1.387		0.500
Anxiety & depression (HADS); *linear regression*	SF-PCS			-0.202 (-0.317 – 0.087)	0.001
	SF-MCS			-0.971 (-1.073 – -0.078)	< 0.001
Pain catastrophizing (PCS); *linear regression*	SF-PCS			-0.148 (-0.217 – -0.079)	< 0.001
	SF-MCS			-0.365 (-0.441 – -0.290)	<0.001
Somatization (SCL-90-SOM); *linear regression*	SF-PCS			-0.384 (-0.474 – -0.294)	< 0.001
	SF-MCS			-0.285 (-0.396 – -0.174)	< 0.001
Current pain intensity (VAS); *linear regression*	SF-PCS			-0.145 (-0.174 – -0.116)	< 0.001
	SF-MCS			-0.042 (-0.080 – -0.004)	0.030

CI = confidence interval. For abbreviations of questionnaires: see table 4.1.

5

Prognostic factors in the long-term evaluation of chronic, unexplained pain (PROFILE-PAIN): a prospective cohort study

Tom J. Snijders
Albert J.M. van Wijck
Linda M. Peelen
Johannes W.G. Jacobs
Laurien L. Teunissen
Dieuwke S. Veldhuijzen
Jan van Gijn

Submitted for publication

ABSTRACT

Chronic, unexplained pain (CUP) is a common clinical problem which is characterized by chronic pain in the absence of an identifiable medical cause. Predicting a favorable or unfavorable outcome in these patients has substantial clinical value in choosing the proper therapeutic strategy. Several psychological and sociodemographic factors are associated with pain severity and health-related quality of life (HRQOL) in cross-sectional studies, and with the transition from acute to chronic pain, but data on the prognostic value of these factors for the maintenance or improvement of CUP are limited. We performed a prognostic study in 422 CUP patients by collecting baseline data on several putative prognostic factors and measuring pain severity and HRQOL at 16-month follow-up. We found that a clinically important decrease of pain severity occurred in 34% of patients during follow-up. The only significant prognostic factor for such a pain decrease was a high baseline pain intensity. Baseline predictors for poor HRQOL at follow-up were male gender, high baseline HRQOL and (for physical HRQOL) high baseline pain intensity. The modest explanatory power of our models suggests that a large part of the variation in changes of pain severity and HRQOL over time in CUP is dependent on other factors than those we studied.

INTRODUCTION

Chronic pain is characterized by the persistence of pain past the healing phase following an injury.[1] In a substantial part of chronic pain patients, no nociceptive or neuropathic source of pain can be identified at all. Such chronic, unexplained pain (CUP) is a common clinical problem, both in the general population,[2] and in hospital outpatient clinics.[3] Although clinicians often distinguish many different CUP syndromes (also known as functional pain syndromes), such as fibromyalgia or temporomandibular joint dysfunction, overlap of symptom profiles as well as psychological and pathophysiological characteristics support the idea that these syndromes are part of a continuous spectrum of CUP rather than separate entities.[4-7] Since the exact cause of CUP is – by definition – unknown, available treatment strategies are mostly empirical in nature, with varying success rates.

CUP may be self-limiting, but a substantial proportion of patients will continue to suffer from symptoms over time. Previous studies on prognosis in a variety of non-malignant pain syndromes show a recovery rate of pain in the middle-to-long-term (>12 months) that ranges from 15 to 68%.[8-12] One of the causes for this wide range may be differences in baseline duration of pain symptoms (acute or already chronic). For proper counseling and treatment, exact knowledge on the prognosis of an individual patient with CUP is of great value. Both in therapeutic research and in clinical practice, there is a need for tools that aid in distinguishing patients with a favorable prognosis from those who will remain stable or even worsen (and may thus profit most from additional treatments). Previous prognostic studies have focused mostly on the transition from acute to chronic pain, but much less is known about prognostic factors for pain that is already chronic. Studies on post-surgical pain demonstrated that prognostic factors for the transition from acute to chronic pain are not necessarily predictive of the maintenance of chronic pain.[13,14]

Many pain-related, demographic, and psychological factors have been identified or implied as prognostic factors for recovery or persistence of pain in previous studies on spinal pain and other forms of musculoskeletal pain.[9-12,15-20] The number of studies on prognostic factors in the spectrum of CUP syndromes, however, is limited.

We performed the PROFILE-PAIN-study (PROgnostic Factors In the Long-term Evaluation of chronic, unexplained PAIN), a prospective cohort study among CUP patients, with the aim to (1) determine prognosis of pain and HRQOL in the middle-to-long-term (16 months); (2) evaluate the prognostic value of several clinical and psychological factors for a favorable *versus* a stable or worsened outcome after 16 months. In a cross-sectional analysis of the same cohort of patients, we found that several, mostly psychological, factors are associated with pain severity and HRQOL. Pain severity was associated with physical, but not with mental aspects of HRQOL.[Chapter 4 of this thesis] On the basis of these previous results, we hypothesize that psychological

factors and pain severity are baseline predictors of 16-month prognosis of pain and HRQOL in CUP.

MATERIALS AND METHODS

Patients and inclusion procedure

We included patients from outpatient clinics in the University Medical Center Utrecht, The Netherlands, (departments of Neurology, Pain Medicine, and Rheumatology) and the St Antonius Hospital Utrecht/Nieuwegein, The Netherlands which is a large general teaching hospital (departments of Neurology, Pain Medicine). We screened patients for eligibility at their first visit to the outpatient clinic, by screening the referral letters beforehand if possible, and by reviewing patient records after the consultation in all cases. In- and exclusion criteria have been described in detail previously.[Chapter 4 of this thesis]

Inclusion criteria were:

- Adult patients (18 years or older) with pain lasting at least three months.
- No conventional medical cause could be determined on routine medical evaluation. Routine medical evaluation consisted of history taking, physical examination, and review of previous medical history by the treating physician. Ancillary investigations were performed at the treating physician's discretion, in accordance with professional standards and (inter-)national guidelines; no extra ancillary studies were performed for the purpose of this study.
- A diagnosis of a specific functional pain syndrome, e.g. fibromyalgia or temporomandibular joint dysfunction, was allowed, since these diagnoses are part of the spectrum of CUP. However, such a diagnosis was not necessary for inclusion. Patients who met the Dutch criteria for non-specific low back pain were also enrolled;[21] this group included patients with pain at or near the sacro-iliac joint(s) or the zygo-apophysial joints. Mild degenerative changes on imaging studies of the low back did not lead to exclusion since such imaging findings are common and poorly correlated with clinical symptoms.[22]
- Sufficient knowledge of the Dutch language.

If patients met inclusion criteria according to the treating physician and the study team, one of the team members informed the patient about the study and asked him/her to participate, either during the clinic visit or by telephone. The patients then received further written information and the questionnaires. Non-responders received up to two reminders, by telephone or by mail. We included patients in baseline- and follow-up-analysis if they completed and returned at

least part of the baseline questionnaires. For patients who completed baseline questionnaires but did not return follow-up questionnaires, we imputed the missing follow-up data (see below).

This study was approved by the Medical Ethics Review Boards of the involved centers. No written informed consent was required for this questionnaire-based study.

Baseline evaluation

We collected the following data at baseline:

- Medical records: age and gender. We also recorded current pain diagnosis (including functional pain syndromes) and previous pain diagnosis if available, but most involved physicians did not routinely note the presence or absence of these syndromes in their medical records.
- The McGill Pain questionnaire, Dutch language version (MPQ-DLV): pain location from drawings on pain mannequins to allow a classification of 'chronic widespread pain (CWP)' according to criteria of the American College of Rheumatology;[23] pain duration; visual analogue scale (VAS) ratings for current pain intensity as well as mildest and worst pain, with a range from 0 ("no pain at all") to 100 mm ("unbearable pain").[24,25]
- The Multidimensional Pain Inventory, Dutch language version (MPI-DLV):[26] we calculated the coping profile with available standard scoring software, on the basis of previously published factorial analysis. This resulted in a Dysfunctional, Interpersonally Distressed, Average, Adaptive Coper or Anomalous subtype (or 'profile').[27]
- Pain Catastrophizing Scale, Dutch Version (PCS):[28] we calculated the total score for pain catastrophizing.
- Hospital Anxiety and Depression Scale (HADS), Dutch version:[29,30] the total HADS score was calculated as a compound measure for anxiety and depression.
- Symptoms Check List-90, somatization subscale (SCL-90-SOM),[31] Dutch version (Swets & Zeitlinger b.v., Lisse, Netherlands): we calculated the total SCL-90-SOM score as a measure of the tendency for somatization.
- A self-designed questionnaire: current and previous treatment for pain symptoms (categorized as (a) medication, (b) physical therapy, (c) invasive procedures or transcutaneous electrical nerve stimulation (TENS), or (d) multidisciplinary pain management program); current or past involvement in a medicolegal procedure for (financial) compensation in relation to pain; work status, including sick leave and disability compensation.

- The Short Form-36 health questionnaire, Dutch Version (SF36):[32] The Mental and Physical Component Summary (SF-MCS and SF-PCS) scores served as measures for HRQOL. For analysis, we standardized the SF-MCS and SF-PCS scores by means of Dutch reference data.[33]

For each of the scales and questionnaires, we only calculated the total or compound score if a minimum number of items (as stated in the different validation studies) was completed.

Evaluation at follow-up

All patients received follow-up questionnaires, which we sent in batches every two months; they were returned after a median interval of 15.8 months (interquartile range 14.7 – 17.3) after baseline measurement. We recorded the following questionnaires and corresponding outcome measures:

- MPQ-DLV: we only recorded the VAS for current pain intensity, mildest pain and maximum pain.
- SF36: again, we calculated the SF-MCS and SF-PCS scores, standardized on the basis of Dutch reference data.
- Therapy during follow-up: we asked patients to complete the same self-designed questionnaire that we used at baseline about treatments they underwent during the follow-up period.

Statistical analysis

The primary outcome measures in this study were:

- A clinically important decrease in pain severity (further labeled pain decrease-outcome) at follow-up, defined as a decrease in VAS-score between baseline and follow-up of at least 30% or at least 20 mm.[34] We chose to use a dichotomous outcome measure of change in VAS score to increase the clinical relevance of this analysis: the finding of a statistically significant predictor may directly be interpreted as a factor that is predictive of a clinically meaningful decrease in pain intensity.
- Physical HRQOL on the SF-PCS.
- Mental HRQOL on the SF-MCS.

A secondary (exploratory) outcome measure was the absolute value of the VAS-score at follow-up (continuous outcome measure). We included this exploratory outcome measure to examine the prognostic factors for pain intensity in CUP in greater detail, especially the relationship between the baseline VAS score and that at follow-up.[35,36]

From the baseline questionnaires, we used 10 variables as possible prognostic factors for the VAS outcome measure (table 5.3); analyses for the HRQOL outcome included the baseline HRQOL as an 11th variable. Certain analyses also included current and previous therapy at baseline (4 variables) as prognostic variables.

We first performed univariable analysis of the association between the prognostic factors and the primary outcome measures. For the (dichotomous) pain decrease-outcome we used Pearson's chi-square tests for categorical variables and simple logistic regression for continuous variables.

For the continuous outcome measures (physical and mental HRQOL), we used regression analysis for all (categorical and continuous) variables. The regression analyses mostly consisted of linear regression; inspection of scatterplots led to variable conversion for age (inverted) and pain duration (logarithmic) to better fit the observed association.

Before multivariable analysis, we calculated correlation coefficients for each pair of determinants in order to check for collinearity; a correlation coefficient >0.4 was considered to represent relevant collinearity. Subsequent multivariable analysis consisted of multiple logistic regression analysis for the pain decrease-outcome, and of multivariable linear regression for the primary HRQOL outcome measures and the secondary outcome measure of absolute VAS-score (we did not perform univariable analyses for this secondary outcome measure to prevent redundancy and overtesting). In all multivariable analyses, we entered all variables in the regression model (we did not perform pre-selection); in case of relevant collinearity between two determinants, we omitted one of these two from the model.

Since current and previous therapy at baseline may be important both as a negative marker for disease severity (patients with more severe pain are likely to receive more therapies), and as a positive factor (through the effect of therapy), we performed the analysis for the pain decrease-outcome twice, both with and without addition of 'therapy at baseline' as a categorical variable. For all multivariable analyses, we calculated R^2-values as measures for the amount of explained variance.

We imputed missing values by means of multiple imputation; this method of handling missing values minimizes the risk of bias that is inherent to other methods, especially when the data are not 'missing completely at random'.[37] We performed ten imputations and all reported data are based on the pooled results for the ten imputations. All analyses were performed in SPSS version 19.0. A p-value of 0.05 was considered significant.

RESULTS

Patient inclusion and baseline characteristics

Of 748 eligible patients, 422 (56%) completed baseline questionnaires and were included in the study (figure 5.1). We did not obtain follow-up data for 151 of 422 patients, mostly because they did not return follow-up questionnaires (non-response; 125 patients); another 26 patients refused to participate, because of lack of time or interest (12), trouble completing the written questionnaires (4), health problems (5) and other reasons (5). The remaining 271 patients completed the follow-up questionnaires.

A comparison of the non-responders and responders at follow-up shows that they differed significantly in age (non-responders *versus* responders: 47.8 versus 51.0 years, mean difference -3.3, 95%-confidence interval (CI) -6.2 – -0.4, p=0.026, Student's t-test), duration of pain symptoms (76.0 *versus* 106.7 months, mean difference -30.8, 95%-CI -52.4 – -9.1, p=0.005) and total PCS score for catastrophizing (24.4 *versus* 20.9, mean difference 3.5, 95%-CI 1.0 – 5.9, p=0.006). We then imputed missing data for the non-responders by means of multiple imputation to avoid non-response bias. In the questionnaires we received, the overall rate of missing data for the prognostic variables and outcome measures was 4.3%. We imputed these missing data as well.

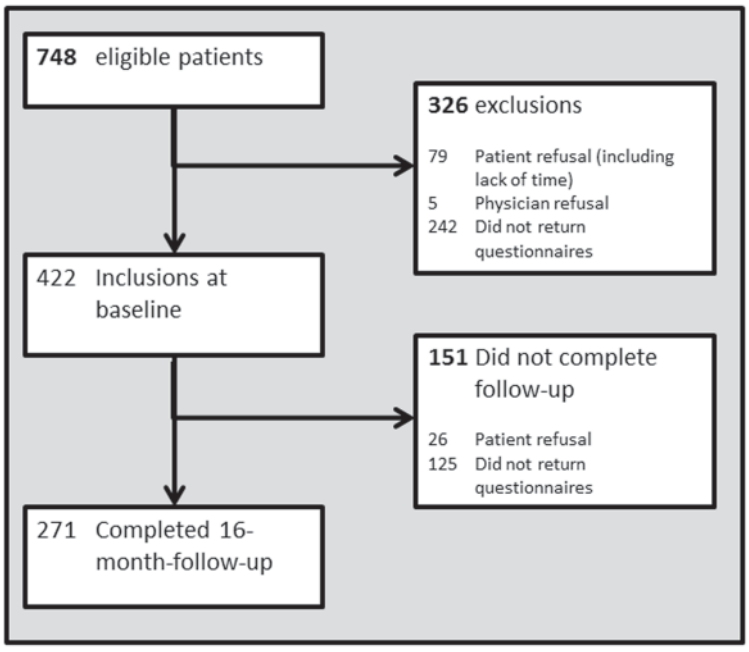

Figure 5.1 Flowchart of patient inclusion and participation at follow-up.

Baseline characteristics are given in table 5.1. Most patients were female (68.5%). Mean age was 49.9 years. Median pain duration was 4 years and 28.9% suffered from widespread pain. More details on the baseline characteristics of the patient group have been published elsewhere.[Chapter 4 of this thesis]

Table 5.1 Patient characteristics (prognostic variables) at baseline. Data presented are number of patients, with percentage of total between brackets, unless specified otherwise. The presented data are derived from the imputed data set.

Demographic variables	
Females	289 (68.5%)
Age in years (mean +/- SD)	49.9 +/- 14.6
Pain duration in months (median (IQR))	48 (18-120)
Widespread pain	122 (28.9%)
Involvement in a legal conflict/procedure in relation to pain	
Current procedure	48 (11.4%)
Past procedure	43 (10.2%)
Therapy before and at the time of baseline measurement	
Physical	364 (86.3%)
Invasive and TENS	209 (49.5%)
Multidisciplinary/rehabilitation	50 (11.8%)
Medication	343 (81.3%)
Questionnaires	
Hospital Anxiety and Depression Scale (HADS) score (median (IQR))	13.0 (8.0 – 17.0)
Pain Catastrophizing Scale (PCS) score (median (IQR))	20.0 (12.0 – 30.0)
Symptom Check List, somatization subscale (SCL-90-SOM) (median (IQR))	26.0 (20.0 – 33.0)
Multidimensional Pain Inventory (MPI), coping profile	
Anomalous	44 (10.4%)
Adaptive coper	70 (16.6%)
Average	114 (27.0%)
Interpersonally distressed	79 (18.7%)
Dysfunctional	115 (27.3%)
Pain and health-related quality of life	
Current pain, Visual Analogue Scale in mm (median (IQR))	52.0 (28.0 – 70.0)
Short Form 36 Physical Component Subscale (SF-PCS) score (mean ± SD)	34.4 +/- 8.7
Short Form 36 Mental Component Subscale (SF-MCS) score (mean ± SD)	44.9 +/- 10.1

IQR = interquartile range; SD = standard deviation; TENS = transcutaneous electrical nerve stimulation.

Outcome at 16-month follow-up

Outcome at 16-month follow-up is summarized in table 5.2. Of all patients, 33.6% had a clinically meaningful decrease in VAS-score at follow-up (pain decrease-outcome).

Prognostic factors for a clinically important decrease in pain severity (pain decrease-outcome)

In univariable analysis (table 5.3), none of the tested determinants were significantly associated with the pain decrease-outcome at 16-month follow-up, except for the current pain intensity at baseline on the VAS; patients with high baseline VAS-scores were more likely to have a clinically important decrease in pain at follow-up than patients with low baseline VAS-scores, with an odds ratio (OR) of 1.014 (95%-CI 1.001 – 1.027, p=0.038) for each mm of VAS increase; this corresponds to an 1.148 times increased odds with each 10 mm of VAS increase).

For multiple logistic regression analysis (table 5.4), we included all variables in the model except for anxiety/depression (HADS-score), since anxiety/depression and catastrophizing displayed relevant collinearity (Pearson r^2= 0.474, p<0.0005). In the regression model, only current pain intensity at baseline was a significant predictor of the pain decrease-outcome (OR 1.019, 95%-CI 1.004 – 1.034, p=0.016); high VAS scores at baseline were associated with better chances of the pain decrease-outcome at follow-up. We repeated the multiple regression both with and without 'therapy at baseline' as a determinant; baseline current pain intensity was the only significant factor in both models and explanatory power was comparable for the model with therapy (mean Nagelkerke R^2 0.109) and without therapy (Nagelkerke R^2 0.098).

Table 5.2 Outcome measures at 16-month follow-up. The data included are derived from the imputed data set.

Pain	
Current pain, VAS in mm (median (IQR))	46.5 (22.5 – 67.5)
Difference in current pain ($VAS_{1\ year}$ minus $VAS_{baseline}$) in mm (median (IQR))	-4.0 (-20.0 – 12.0)
Clinically important decrease in pain severity (number of patients (percentage))*	142 (33.6%)
Health-related quality of life	
Short Form 36 Physical Component Subscale (SF-PCS) score (mean ± SD)	36.3 +/- 8.8
Short Form 36 Mental Component Subscale (SF-MCS) score (mean ± SD)	45.4 +/- 8.3

IQR = interquartile range; SD = standard deviation. * = a decrease of at least 30% from baseline, or at least 20 mm.

Table 5.3 Predictors of a clinically important decrease in 16-month current pain intensity (pain decrease-outcome): Univariable analysis. Logistic regression analysis was used for continuous determinants; we used chi-square tests for categorical determinants.

Determinant (baseline)	Categorical determinants % of patients with a VAS-decrease		Odds ratio (95%-CI)*	p-value
Gender	Female:	35%	1.076 (0.943 – 1.228)	0.291
	Male:	30%	1.0 (reference)	
Age (y)			0.999 (0.977 – 1.021)	0.896
Pain duration (months)			0.999 (0.997 – 1.001)	0.199
Current pain at baseline (VAS in mm)			1.014 (1.001 – 1.027)	0.038
Chronic widespread pain (CWP)	CWP:	31%	0.825 (0.525 – 1.298)	0.404
	No CWP:	35%	1.0 (reference)	
Coping profile/MPI cluster	Anomalous:	38%	1.0 (reference)	0.944
	Adaptive coper:	31%	0.726 (0.328 - 1.604)	
	Average:	34%	0.863 (0.419 - 1.775)	
	Interpersonally distressed:	32%	0.781 (0.361 - 1.688)	
	Dysfunctional:	34%	0.855 (0.415 - 1.759)	
Legal procedure	Never:	35%	1.0 (reference)	0.572
	Previous:	29%	0.779 (0.388 – 1.565)	
	Current:	29%	0.746 (0.383 - 1.455)	
Anxiety & depression (HADS)			0.986 (0.937 – 1.038)	0.578
Pain catastrophizing (PCS)			1.002 (0.981 – 1.025)	0.829
Somatization (SCL-90-SOM)			0.994 (0.963 – 1.027)	0.717
Therapy at or before baseline measurement				
Therapy: physical	No:	40%	1.0 (reference)	0.271
	Yes:	33%	0.727 (0.411 – 1.286)	
Therapy: invasive/TENS	No:	32%	1.0 (reference)	0.417
	Yes:	35%	1.183 (0.790 – 1.773)	
Therapy: multidisciplinary	No:	33%	1.0 (reference)	0.365
	Yes:	39%	1.323 (0.721 – 2.426)	
Therapy: medication	No:	31%	1.0 (reference)	0.543
	Yes:	34%	1.177 (0.695 – 1.993)	

* Odds ratios are calculated as Exp (B) for continuous determinants. CI = confidence interval; df = degrees of freedom. See table 5.1 for abbreviations of questionnaires.

Table 5.4 Prognostic factors for a clinically important decrease in pain severity (the pain decrease-outcome) at 16-month follow-up: Multiple logistic regression model. Anxiety/depression (HADS-score) was omitted from the model because of collinearity

Determinant (baseline)	Odds ratio (95%-CI)	p-value
Gender		0.439
Male	1.0 (reference category)	
Female	1.275 (0.684 – 2.376)	
Age (y)	1.001 (0.976 – 1.026)	0.948
Pain duration (months)	0.999 (0.996 – 1.001)	0.294
Current pain intensity at baseline (VAS)	1.019 (1.004 – 1.034)	0.016
Chronic widespread pain *	0.767 (0.355 – 1.658)	0.489
Coping profile/MPI cluster		
Anomalous	1.0 (reference category)	
Adaptive coper	0.650 (0.127 – 3.335)	0.589
Average	0.790 (0.232 – 2.696)	0.698
Interpersonally distressed	0.664 (0.142 – 3.120)	0.588
Dysfunctional	0.622 (0.157 – 2.471)	0.484
Legal procedure		
No procedure	1.0 (reference category)	
Current procedure (at baseline)	0.666 (0.265 – 1.675)	0.383
Previous procedure (at baseline)	0.665 (0.208 – 2.126)	0.479
Pain catastrophizing (PCS)	0.991 (0.968 – 1.013)	0.410
Somatization (SCL-90-SOM)	0.990 (0.953 – 1.028)	0.589
Therapy at or before baseline measurement		
Physical *	0.700 (0.334 – 1.466)	0.341
Invasive/TENS *	1.127 (0.681 – 1.864)	0.641
Multidisciplinary *	1.230 (0.482 – 3.141)	0.658
Medication *	1.175 (0.602 – 2.291)	0.634

CI = confidence interval. * = the odds ratio (OR) represents the OR for the presence of the determinant in question, e.g. for chronic widespread pain (CWP) the OR for the absence of CWP is 1.0 (reference category) and the presented OR in the table represents the OR for the presence of CWP. See table 5.1 for abbreviations of questionnaires.

To explore the role of treatments received during the follow-up period on the occurrence of the pain decrease-outcome, we performed a post-hoc analysis in which we repeated the multiple logistic regression analysis for the pain decrease-outcome with addition of the treatment during the follow-up period as determinants, categorized as for the baseline treatment variables. Again, we did not find any significant prognostic variables except for baseline pain intensity (VAS); no significant prognostic effect of treatment during follow-up could be identified.

Prognostic factors for pain intensity (absolute VAS-score) at 16-month follow-up

To further explore the determinants of pain intensity at follow-up, we performed multiple linear regression analysis with the absolute VAS-score at follow-up as the (secondary) outcome measure. Current pain intensity (VAS-score) at baseline was the only significant prognostic factor in the model; high baseline pain intensity was associated with high pain intensity at follow-up (B=0.406, 95%-CI 0.257 – 0.555, p<0.001).

Prognostic factors for health-related quality of life

In univariable analysis (table 5.5), the following baseline factors were associated with poor physical HRQOL at follow-up: long pain duration, presence of chronic widespread pain, a previous (but not a current) medicolegal procedure, high anxiety/depression score, high catastrophizing score, high somatization score, high current pain intensity and poor baseline physical HRQOL.

The multiple linear regression model for physical HRQOL (which did not include anxiety/depression because of collinearity with PCS) showed that male gender, high current pain intensity, and poor baseline physical HRQOL were all independently associated with poor physical HRQOL at follow-up (table 5.6). The mean adjusted R^2 (as a measure of the model's explanatory power) was 0.287.

In univariable analysis, factors associated with poor mental HRQOL at follow-up were: male gender, high anxiety/depression score, high catastrophizing score, high somatization score, and poor baseline mental HRQOL (table 5.5).

In multiple regression analysis, poor mental HRQOL at follow-up was associated with male gender and with poor baseline mental HRQOL (table 5.6), with a mean adjusted R^2 of 0.184. Since anxiety/depression, catastrophizing, and baseline mental HRQOL showed strong collinearity, we did not include anxiety/depression in the first analysis (table 5.6); we then performed a second analysis in which we also omitted catastrophizing. We did not find differences in significant determinants between these two analyses.

Table 5.5 Determinants of the 16-month physical (SF-PCS) and mental (SF-MCS) component subscales of HRQoL: Univariable (linear regression) analysis

Determinant (baseline)	Physical HRQOL (SF-PCS)		Mental HRQOL (SF-MCS)	
	β-value (95%-CI)	p-value	β-value (95%-CI)	p-value
Gender (male vs female)	1.333 (-0.496 – 3.162)	0.153	3.489 (1.503 – 5.475)	0.001
Age (y)	-0.008 (-0.068 – 0.052)	0.793		0.348
Inverted (SF-MCS only)			64.37 (-28.89 – 157.64)	0.176
Pain duration (months; log-converted)	-2.801 (-4.368 – -1.234)	< 0.001	-0.922 (-2.415 – 0.570)	0.226
Chronic widespread pain (present vs absent)	-4.128 (-6.124 – -2.132)	< 0.001	0.201 (-1.621 – 2.023)	0.829
Coping profile/MPI cluster (separately per cluster)				
Anomalous	0.0 (reference category)		0.0 (reference category)	
Adaptive coper	1.417 (-3.175 – 6.010)	0.549	3.028 (-1.026 – 7.081)	0.149
Average	-1.245 (-5.168 – 2.679)	0.537	0.559 (-3.204 – 4.342)	0.769
Interpersonally distressed	-0.384 (-4.427 – 3.659)	0.853	-1.736 (-5.798 – 2.326)	0.407
Dysfunctional	-2.505 (-6.474 – 1.463)	0.221	-0.480 (-4.479 – 3.519)	0.815
Legal procedure				
No procedure	0.0 (reference category)		0.0 (reference category)	
Current procedure (at baseline)	-1.704 (-4.654 – 1.246)	0.259	-2.772 (-5.598 – 0.054)	0.056
Previous procedure (at baseline)	-3.886 (-7.220 – -0.552)	0.024	-0.232 (-3.264 – 2.800)	0.881
Anxiety & depression (HADS)	-0.145 (-0.278 – -0.013)	0.032	-0.436 (-0.565 – -0.307)	< 0.001
Pain catastrophizing (PCS)	-0.078 (-0.152 – -0.003)	0.041	-0.165 (-0.235 – -0.095)	< 0.001
Somatization (SCL-90-SOM)	-0.232 (-0.332 – -0.132)	< 0.001	-0.156 (-0.253 – -0.058)	0.002
Current pain intensity at baseline (VAS)	-0.106 (-0.138 – -0.074)	< 0.001	-0.010 (-0.047 – 0.026)	0.575
Physical HRQoL at baseline (SF-PCS)	0.524 (0.430 – 0.617)	< 0.001		
Mental HRQoL at baseline (SF-MCS)			0.326 (0.246 – 0.406)	< 0.001

CI = confidence interval. See table 5.1 for abbreviations of questionnaires.

Table 5.6 Determinants of the 16-month physical (SF-PCS) and mental (SF-MCS) component subscales of HRQoL: Multiple linear regression analysis

Determinant (baseline)	Physical HRQOL (SF-PCS)		Mental HRQOL (SF-MCS)	
	β-value (95%-CI)	p-value	β-value (95%-CI)	p-value
Gender (male vs female)	1.694 (0.053 – 3.336)	0.043	2.252 (0.243 – 4.260)	0.028
Age (y)	-0.006 (-0.063 – 0.051)	0.839		
Inverted (SF-MCS only)			48.63 (-44.99 – 142.25)	0.308
Pain duration (months; log-converted)	-1.432 (-2.866 – 0.001)	0.0502	-0.349 (-1.842 – 1.144)	0.646
Chronic widespread pain (present vs absent)	-1.151 (-3.197 – 0.896)	0.269	0.362 (-1.549 – 2.274)	0.709
Coping profile/MPI cluster (separately per cluster)				
Anomalous	0.0 (reference category)		0.0 (reference category)	
Adaptive coper	0.761 (-2.798 – 4.319)	0.672	1.249 (-2.857 – 5.356)	0.542
Average	1.054 (-2.239 – 4.347)	0.526	0.296 (-3.803 – 4.395)	0.884
Interpersonally distressed	1.888 (-1.730 – 5.506)	0.301	-0.888 (-5.469 – 3.694)	0.694
Dysfunctional	0.295 (-2.994 – 3.583)	0.859	-0.319 (-4.976 – 4.337)	0.889
Legal procedure				
Current procedure (at baseline)	0.611 (-1.846 – 3.068)	0.626	-1.702 (-4.370 – 0.967)	0.210
Previous procedure (at baseline)	-1.302 (-4.435 – 1.832)	0.410	0.015 (-3.041 – 3.070)	0.992
Pain catastrophizing (PCS)	0.038 (-0.034 – 0.110)	0.304	-0.054 (-0.130 – 0.023)	0.170
Somatization (SCL-90-SOM)	-0.044 (-0.149 – 0.062)	0.416	-0.099 (-0.204 – 0.005)	0.062
Current pain intensity at baseline (VAS)	-0.043 (-0.080 – -0.005)	0.025	0.018 (-0.020 – 0.055)	0.357
Physical HRQoL at baseline (SF-PCS)	0.429 (0.315 – 0.543)	<0.001		
Mental HRQoL at baseline (SF-MCS)			0.241 (0.153 – 0.329)	<0.001

CI = confidence interval. See table 5.1 for abbreviations of questionnaires.

DISCUSSION

The main findings in this prospective cohort study on the 16-month prognosis of pain severity and HRQOL in patients with chronic, unexplained pain are:

1. A clinically important decrease of pain severity during follow-up occurred in 34% of CUP patients. We did not identify any baseline factors that were correlated with pain intensity at follow-up except for baseline pain intensity, with high baseline pain severity predicting a better chance of the pain decrease-outcome.
2. Baseline predictors for poor physical health-related quality of life (HRQOL) at 16-month follow-up are male gender, high pain intensity and high baseline physical HRQOL. In univariable analysis, we also found an association of poor physical HRQOL at follow-up with the presence of widespread pain, previous involvement in a pain-related medicolegal procedure and high scores for somatization, catastrophizing and anxiety/depression. However, these associations could not be reproduced in multivariable analysis, suggesting that the associations of these factors with physical HRQOL at follow-up are better accounted for by other factors (gender, pain duration, pain intensity and baseline physical HRQOL).
3. Baseline predictors for poor mental HRQOL at follow-up are male gender and baseline mental HRQOL. The associations of mental HRQOL at follow-up with baseline coping profile, catastrophizing, somatization and anxiety/depression in univariable analysis were not significant in multiple regression analysis.
4. Explanatory power of our models was poor, suggesting that a large part of the variation in changes of pain severity and HRQOL is dependent on other factors than those we studied.

Baseline pain intensity (VAS-score) was the only determinant for a clinically important pain decrease at follow-up; high baseline pain intensity was also associated with high absolute pain intensity at follow-up. In other words, CUP patients with high levels of baseline pain have a better chance of experiencing a clinically important pain decrease over time than those patients with low baseline pain, but they will generally still have more pain at follow-up. The positive relation between baseline pain severity and later pain severity has been reported before, for example in studies of spinal pain.[11,12,38]

Previous studies have shown that changes in pain severity, as well as the minimum VAS-decrease that patients consider meaningful, are dependent on the magnitude of baseline pain ratings.[34,35] For this reason, and to increase the clinical utility of our study, we chose a relative measure of pain severity (VAS-decrease of at least 30% or at least 20 mm) that has been shown to represent a clinically important difference.[34] The choice of this dichotomous

outcome measure might theoretically lead to decreased statistical power in the identification of prognostic factors. However, the secondary analysis of absolute VAS-score at follow-up confirmed the finding that – other than baseline pain intensity – none of the studied factors has prognostic value for pain intensity at follow-up.

Our findings do not confirm previous prognostic studies on pain intensity in several clinical pain states that report a prognostic value of factors such as age,[11,12] duration of pain symptoms,[10,15] involvement in pain-related medicolegal conflicts in relation to pain,[19] anxiety and depression,[16-18] hysteria/somatization, worrying about disease,[9] socio-occupational factors and a large number of painful body areas.[8] In a meta-analysis on the course of subacute low back pain, negative prognostic factors at baseline were the presence of non-organic signs, maladaptive pain coping, psychiatric comorbidity, high functional impairment and low general health status.[20]

Several explanations for the discrepancies between the current study and previous studies are possible:

- The populations are different. Most previous studies focus on prognostic factors in acute or subacute pain (<3 months) and therefore investigate risk factors for transition from acute to chronic pain,[10-12,15,16,18-20] whereas our study is one of the few that studied patients with pain that was already chronic (median 4 years) at baseline.[9,17] These patients have often undergone many previous treatments with unsatisfactory effect. For this population, we have previously shown that several factors (somatization, catastrophizing and a dysfunctional coping style) were all independently related to pain severity in a cross-sectional analysis.[Chapter 4 of this thesis] The combination of our previous and current findings implies that these determinants indeed contribute to (development of) pain severity in CUP, but that they do not have an additional predictive value for changes in pain severity over time. This discrepancy between prognostic factors for development *versus* maintenance of chronic pain is in line with previous work in postsurgical pain.[13,14] It may be speculated that the factors that determine maintenance (and possibly development) of CUP lie beyond the usual clinical-epidemiological risk factors and should be sought at the level of mechanisms of pain amplification in the nervous system – which can be studied by measuring intrinsic pain sensitivity – since the role of these mechanisms in CUP syndromes is increasingly recognized.[39,40]
- A decrease in pain severity in the context of pain that is already chronic may simply represent a random fluctuation of pain. Such fluctuations are expected to be directed downward (pain decrease) in patients with high baseline pain

and upward in patients with low baseline pain (regression to the mean).[41]

- Despite the observational study design, many patients received treatments during the study period as part of normal clinical practice, which may theoretically have caused a decrease in pain. However, we did not find such treatment effects in exploratory analysis, suggesting that the limited number of prognostic factors in our analysis cannot be explained by treatment effects (although our study was not designed to draw definite conclusions on the effect of treatments for CUP).
- Insufficient study power could be considered as the cause for these negative findings. Since we found that 142 patients experienced the pain decrease-outcome, our study was powered to examine 142/10 (events per factor) = 14 factors.[42] In the pain decrease-analysis, we studied 10 variables corresponding to 14 factors (because categorical variables represent more than one factor), meaning that this analysis was sufficiently powered. We performed extra analyses that included therapy as determinants (4 extra factors), making these analyses slightly more vulnerable to type-II-error; however, the results of these extra analyses do not suggest that this is the case.

Because of the poor explanatory power and the limited number of significant prognostic factors of the prognostic model for the pain decrease-outcome, we did not perform further model reduction for development of a clinical prediction rule.

In the analysis of prognostic factors for mental and physical HRQOL at follow-up, we found a discrepancy between the large number of factors that were associated with mental and physical HRQOL at follow-up in univariable analysis, and the much smaller number of factors that survived multivariable testing. This may be explained by a strong association of the baseline factors involved (mostly psychological factors: coping profile, anxiety/depression, catastrophizing, somatization) with baseline scores of mental and physical HRQOL, an association that emerged both from the cross-sectional analysis of this same cohort[Chapter 4 of this thesis] and from a study on somatoform pain disorder (for the factors coping and catastrophizing).[43] Analogous to our findings for the pain decrease-outcome, it is possible that these psychological factors contribute to development of HRQOL but have no added value over the baseline HRQOL scores in predicting further evolution of HRQOL in the chronic phase. We did find a significant effect of gender on physical and mental HRQOL, with men having slightly worse HRQOL than women. A recent study in low back pain also reported this discrepancy between higher prevalence in women but lower HRQOL in men.[44]

The strengths of this study lie in the relatively large cohort and the case definitions that were based on clinical, reproducible criteria, which increases the generalizability of our

findings. By studying many possible prognostic factors simultaneously, including therapy, we were able to study the prognostic value of each determinant independently. Our use of both pain and HRQOL as outcome measures is in line with the IMMPACT recommendation that clinical studies in chronic pain should evaluate multiple outcome domains rather than pain ratings alone.[45]

The relatively high rate of non-response to the questionnaire at follow-up (36%) may be a source of bias. This rate of non-response probably results from the postal questionnaire method; it occurred despite the use of reminders by post and/or telephone. Because of baseline differences between questionnaire responders and non-responders, we imputed missing data including follow-up data for non-responders using multiple imputation to reduce the effects of non-response bias.[37]

Conclusion

About one-third of patients who present in hospital outpatient clinics with chronic, unexplained pain (CUP) experience a clinically important decrease in pain severity over a 16-month follow-up period, but we could not identify factors that predict such a decrease other than the baseline pain intensity. The prognosis of physical and mental health-related quality of life (HRQOL) may be predicted at baseline to some extent on the basis of a limited number of factors: gender, baseline HRQOL and (for physical HRQOL) baseline pain severity. The prognostic value of psychological factors was poor. The modest explanatory power of the studied factors for pain severity may be the consequence of a large role of random fluctuations in the time-course of CUP. Alternatively, other factors than the ones we studied are operative; future studies may improve the prediction of outcome in CUP by expanding the scope of possible prognostic factors to include intermediary (mechanistic) factors such as measures of intrinsic pain sensitivity.

ACKNOWLEDGEMENTS

The authors wish to thank S. Kruis, BSc, for assistance in acquisition and entry of follow-up data; the physicians at the five participating outpatient clinics for their support in inclusion of patients.

REFERENCES

1. Merskey H, Bogduk N, editors. Classification of chronic pain. Second ed. 1994.
2. Verhaak PFM, Kerssens JJ, Dekker J, Sorbi MJ, Bensing JM. Prevalence of chronic benign pain disorder among adults: a review of the literature. Pain 1998;77:231-9.

3. Snijders TJ, de Leeuw FE, Klumpers UMH, Kappelle LJ, van Gijn J. Prevalence and predictors of unexplained neurological symptoms in an academic neurology outpatient clinic - An observational study. J Neurol 2004;251:66-71.

4. Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? Lancet 1999;354:936-9.

5. Snijders TJ, Ramsey NF, Koerselman F, van Gijn J. Attentional modulation fails to attenuate the subjective pain experience in chronic, unexplained pain. Eur J Pain 2010;14:282-10.

6. Nimnuan C, Rabe-Hesketh S, Wessely S, Hotopf M. How many functional somatic syndromes? J Psychosom Res 2001;51:549-57.

7. Mayer EA, Bushnell MC. Functional pain disorders: time for a paradigm shift? In: Mayer EA, Bushnell MC, editors. Functional pain syndromes. 1st ed. Seattle: IASP Press; 2009. p. 531-65.

8. Andersson HI. The course of non-malignant chronic pain: a 12-year follow-up of a cohort from the general population. Eur J Pain 2004;8:47-53.

9. Akerlind I, Hornquist JO, Bjurulf P. Psychological factors in the long-term prognosis of chronic low back pain patients. J Clin Psychol 1992;48:596-605.

10. Bot SD, van der Waal JM, Terwee CB, van der Windt DA, Scholten RJ, Bouter LM, et al. Predictors of outcome in neck and shoulder symptoms: a cohort study in general practice. Spine 2005;30:E459-E470.

11. Hendriks EJ, Scholten-Peeters GG, van der Windt DA, Neeleman-van der Steen CW, Oostendorp RA, Verhagen AP. Prognostic factors for poor recovery in acute whiplash patients. Pain 2005;114:408-16.

12. Karjalainen K, Malmivaara A, Mutanen P, Pohjolainen T, Roine R, Hurri H. Outcome determinants of subacute low back pain. Spine 2003;28:2634-40.

13. Katz J, Asmundson GJ, McRae K, Halket E. Emotional numbing and pain intensity predict the development of pain disability up to one year after lateral thoracotomy. Eur J Pain 2009;13:870-8.

14. Seebach CL, Kirkhart M, Lating JM, Wegener ST, Song Y, Riley LH, III, et al. Examining the role of positive and negative affect in recovery from spine surgery. Pain 2012;153:518-25.

15. Croft P, Pope D, Silman A. The clinical course of shoulder pain: prospective cohort study in primary care. Primary Care Rheumatology Society Shoulder Study Group. BMJ 1996;313:601-2.

16. Dionne CE. Psychological distress confirmed as predictor of long-term back-related functional limitations in primary care settings. J Clin Epidemiol 2005;58:714-8.

17. Lillefjell M, Krokstad S, Espnes GA. Prediction of function in daily life following multidisciplinary rehabilitation for individuals with chronic musculoskeletal pain; a prospective study. BMC Musculoskelet Disord 2007;8:65.

18. Muris JW, Starmans R, Fijten GH, Knottnerus JA. One-year prognosis of abdominal complaints in general practice: a prospective study of patients in whom no organic cause is found. Br J Gen Pract 1996;46:715-9.

19. Rasmussen C, Leboeuf-Yde C, Hestbaek L, Manniche C. Poor outcome in patients with spine-related leg or arm pain who are involved in compensation claims: a prospective study of patients in the secondary care sector. Scand J Rheumatol 2008;37:462-8.

20. Chou R, Shekelle P. Will this patient develop persistent disabling low back pain? JAMA 2010;303:1295-302.

21. Koes BW, Sanders RJ, Tuut MK. [The Dutch Institute for Health Care Improvement (CBO) guideline for the diagnosis and treatment of aspecific acute and chronic low back complaints]. Ned Tijdschr Geneeskd 2004;148:310-4.

22. van Tulder MW, Assendelft WJ, Koes BW, Bouter LM. Spinal radiographic findings and nonspecific low back pain. A systematic review of observational studies. Spine (Phila Pa 1976) 1997;22:427-34.

23. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160-72.

24. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1:277-99.

25. Verkes RJ, Vanderiet K, Vertommen H, Van der Kloot WA, Van der Meij J. De MPQ-DLV: een standaard nederlandstalige versie van de McGill Pain Questionnaire voor België en Nederland. In: Kloot WA van der, Vertommen H, editors. De MPQ-DLV. Een standaard nederlandstalige versie van de McGill Pain Questionnaire. Achtergronden en inleiding.Lisse: Swets & Zeitlinger BV; 1989. p. 57-74.

26. Lousberg R, Van Breukelen G.J., Groenman NH, Schmidt AJ, Arntz A, Winter FA. Psychometric properties of the Multidimensional Pain Inventory, Dutch language version (MPI-DLV). Behav Res Ther 1999;37:167-82.

27. Turk DC, Rudy TE. Toward an empirically derived taxonomy of chronic pain patients: integration of psychological assessment data. J Consult Clin Psychol 1988;56:233-8.

28. Crombez G, Vlaeyen JW, Heuts PH, Lysens R. Pain-related fear is more disabling than pain itself: evidence on the role of pain-related fear in chronic back pain disability. Pain 1999;80:329-39.

29. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997;27:363-70.

30. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.

31. Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale--preliminary report. Psychopharmacol Bull 1973;9:13-28.

32. Ware JE, Jr. SF-36 health survey update. Spine 2000;25:3130-9.

33. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51:1055-68.

34. Farrar JT, Young JP, Jr., LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149-58.

35. Emshoff R, Bertram S, Emshoff I. Clinically important difference thresholds of the visual analog scale: a conceptual model for identifying meaningful intraindividual changes for pain intensity. Pain 2011;152:2277-82.

36. Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. Pain 2000;88:287-94.

37. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006;59:1087-91.

38. Jacob T, Baras M, Zeev A, Epstein L. A longitudinal, community-based study of low back pain outcomes. Spine 2004;29:1810-7.

39. Arendt-Nielsen L, Henriksson KG. Pathophysiological mechanisms in chronic musculoskeletal pain (fibromyalgia): the role of central and peripheral sensitization and pain disinhibition. Best Pract Res Clin Rheumatol 2007;21:465-80.

40. Smith BH, Macfarlane GJ, Torrance N. Epidemiology of chronic pain, from the laboratory to the bus stop: time to add understanding of biological mechanisms to the study of risk factors in population-based research? Pain 2007;127:5-10.

41. Barnett AG, van der Pols JC, Dobson AJ. Regression to the mean: what it is and how to deal with it. Int J Epidemiol 2005;34:215-20.

42. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49:1373-9.

43. Petrak F, Hardt J, Kappis B, Nickel R, Egle UT. Determinants of health-related quality of life in patients with persistent somatoform pain disorder. European Journal of Pain 2003;7:463-71.

44. Ono R, Higashi T, Takahashi O, Tokuda Y, Shimbo T, Endo H, et al. Sex differences in the change in health-related quality of life associated with low back pain. Qual Life Res 2011.

45. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105-21.

PART II

Pathophysiology: pain sensitivity and cerebral pain processing

6

Sensory profiles in chronic, unexplained pain

Tom J. Snijders
Dieuwke S. Veldhuijzen
K. Seng Liem
Anne Catrien Baakman
Jan van Gijn
Albert J.M. van Wijck

Manuscript in preparation

ABSTRACT

Chronic, unexplained pain (CUP) is a common clinical condition which is very difficult to treat since an identifiable medical cause is absent. Diagnostic classification is mostly symptom-based rather than mechanism-based. The limited data on pathophysiological mechanisms underlying CUP point towards augmented cerebral pain processing of somatosensory stimuli. To study sensitivity for different modalities in detail, we performed a quantitative sensory testing (QST) study in 85 CUP patients and 89 healthy controls with a standardized QST protocol. We further correlated QST findings to clinical and psychological variables. CUP patients exhibited an increased sensitivity for painful hot, cold, and pressure stimuli as well as a decreased sensitivity for the detection of non-painful thermal stimuli. Temporal summation of mechanical pain was also increased in CUP. QST data were only partially correlated to clinical and psychological risk factors of chronic pain. In an exploratory factor analysis, we found two factors that explained a substantial part of variance in the QST data: one pain- and temperature-based factor and one for temperature detection and temporal summation of pain. In conclusion, CUP is characterized by a unique sensory phenotype of hypersensitivity for pain across modalities and increased temporal summation of pain – which supports the concept of pain amplification occurring at the supraspinal level – in combination with hyposensitivity to temperature detection. This sensory profile may serve as a starting point for mechanism-based classification of CUP and may be of use as a marker of central sensitization in further research.

INTRODUCTION

Despite continuing scientific and clinical efforts, the efficacy of available treatment for chronic pain is insufficient in a large proportion of patients.[1,2] One possible reason for this limited efficacy is that the choice of therapy for an individual patient is usually based on a symptom-based classification of pain. Because symptom-based classification often correlates poorly with effects of treatment, it has been proposed that a mechanism-based classification of pain may achieve a better match between diagnostic classification and therapeutic outcome.[2,3] The symptom-based approach of pain management is most apparent in patients with chronic, unexplained pain (CUP), in whom no straightforward medical cause for their pain can be found on clinical evaluation. These highly prevalent[4,5] and disabling[6] pain symptoms are often categorized into different idiopathic (or: functional) pain syndromes, such as fibromyalgia or temporomandibular joint disorder (TMD), and treatment is then selected based on this symptom-based diagnostic label. Because these syndromes share many characteristics apart from unexplained pain as the key symptom (overlap in symptom profiles,[7], psychological states,[8,9] and pathophysiological mechanisms),[10] it is proposed that these CUP syndromes form one spectrum rather than separate pathophysiological entities.[11] To advance the treatment of patients within this spectrum, identification and further study of common underlying pain mechanisms is needed.

Several lines of evidence support the theory that central sensitization, the amplification of neural signaling within the central nervous system (CNS), is a key mechanisms in CUP pathophysiology.[12] This evidence includes psychophysical evidence of widespread pain hypersensitivity and other sensory input,[13,14] (which extends beyond the region of clinical pain)[15,16] and the positive effects of centrally acting medication.[17] Functional neuroimaging studies in fibromyalgia reveal abnormal patterns of brain activity in relation to pain processing,[18] most prominently in brain regions involved in descending modulation of pain,[19] supporting the role of abnormal cerebral pain processing in CUP.

To facilitate the classification of CUP in an individual patient according to pain mechanisms such as central sensitization, easily evaluable markers of these mechanisms need to be developed and validated in a clinical-epidemiological context.[20] One obvious candidate marker is the 'sensory phenotype', which can be measured with quantitative sensory testing (QST).[21,22] The separate tests of an individual's experience of sensory stimuli can be combined to form a sensory profile which may differ between different pain conditions.[23,24] Recently, clinical QST protocols have been standardized and reference values are available.[25]

The few previous QST studies in CUP report increased pain sensitivity for one of more modalities (temperature, pressure and mechanical pain) and increased temporal summation of pain in fibromyalgia,[26,27] whiplash-associated pain and TMD.[13,28] Most of the previous QST studies in CUP mostly focused on (one or various) pain thresholds rather than complete sensory

profiles. So far, it is largely unknown whether CUP patients are hypersensitive to noxious stimuli only or also to innocuous stimuli.[29,30]

We performed a QST study in CUP patients and a reference group of healthy volunteers with the aim to determine a comprehensive sensory profile of CUP, and to correlate this sensory profile to clinical and psychological characteristics. Based on the concept of central sensitization as a key pain mechanism in CUP, we hypothesized that CUP patients are hypersensitive to painful (and possibly to non-painful) somatosensory stimuli irrespective of modality.

MATERIALS AND METHODS

Subjects

As part of a prospective cohort study on chronic, unexplained pain, we screened all newly referred patients in outpatient clinics for Neurology, Pain Medicine and Rheumatology of the University Medical Center Utrecht, The Netherlands, for eligibility. Inclusion criteria for this QST-study were:

- Adult patients (18 years or older) with pain lasting for at least three months.
- No conventional medical cause for pain could be determined on routine medical evaluation, or (in case of a known medical cause) the severity of pain far exceeded the severity expected from the known medical cause. Evaluation included history taking, physical examination, and review of medical records by the treating physician. Ancillary investigations were performed at the treating physician's discretion, in accordance with professional standards and (inter-) national guidelines; no extra ancillary studies were performed for the purpose of this study.
- A diagnosis of a CUP syndrome (functional pain syndrome), such as fibromyalgia, TMD, or non-specific low back pain, was allowed, since these diagnoses are part of the spectrum of CUP.[10] However, such a diagnosis was not necessary for inclusion.
- Sufficient knowledge of the Dutch language.
- Pain in (at least) a hand, face or foot, since we performed QST tests in one of these areas. Patients were allowed to have pain outside of these three regions (including widespread pain).
- No skin disease in the QST testing region.
- All consecutive patients that met the abovementioned inclusion criteria were asked to participate.

If patients used analgesic medication, they were allowed to continue using this on the day of QST testing.

We included adult healthy volunteers from databases in our hospital and through locally distributed advertisements. In order to obtain sufficient data for study-specific reference values (see Statistical analysis below), we aimed to include a comparable number of men and women, both below and under 40 years of age. We excluded volunteers with a history of chronic pain, regular or recent (<24 hours preceding QST-testing) use of analgesic or psychoactive medication, hypertension, any relevant neurological, psychiatric or internal disease, or any skin disease in the body regions of interest.

The local medical ethics committee of the University Medical Center Utrecht, The Netherlands, approved the study, in accordance with the Declaration of Helsinki (2008). All participants signed informed consent.

QST procedure

For QST testing, we used a modified version of the QST-protocol published by the German Research Network for Neuropathic Pain (DFNS-protocol).[24] This protocol consists of a concise set of tests on many important somatosensory modalities which can be performed in 30 minutes per body region (hand, foot or face). Details on testing procedure and statistical processing as well as reference values have been published previously.[25] All tests were performed in a testing room of comfortable temperature by one of five trained study group members, all of whom were trained for QST testing by a senior experimenter (DSV).

CUP patients marked their painful body regions on a pain mannequin from the McGill Pain Questionnaire, Dutch Language version.[31] From these clinically painful regions, we then selected a testing region: hand, foot or face, at the left or right side. If a patient had pain in more than one of the possible regions, we selected the hand. In healthy controls, we tested two of the three possible body regions, all on the left side. We tested the hand in all subjects, and either the foot or the face as a second region. Within the tested region, we applied all tests at the dorsum of the hand and foot and on the cheek and zygoma region of the face unless the description of the specific test (below) states otherwise.

The protocol included the following tests:

- Mechanical detection threshold (MDT): After blindfolding the subject, we stimulated the test area with Von Frey filaments (forces between 0.25-512 mN) in five ascending and five descending series. We varied the exact stimulus location within the test region between series. In ascending series, the first filament that was felt was noted. In descending series, the first stimulus that was not felt anymore was noted; if a subject still felt the lowest stimulus (0.25

mN), we noted this value and started the next ascending series again at 0.25 mN. The final MDT is the geometric mean of the values from the ten series.

- Mechanical pain threshold (MPT): Tests consisted of five ascending and five descending series of weighted pinprick stimuli (range 8-512 mN, MRC Systems, Germany). Subjects were blindfolded. Stimulus application during the series was similar to the MDT procedure. We calculated the geometric mean of values from the ten series.
- Wind-up ratio (WUR): Subjects underwent pinprick stimuli of 256 mN (128 mN for the face); we applied five single stimuli and five series of ten stimuli (1 stimulus per second, 10 stimuli within an area of 1 cm^2). Subjects rated the pain caused by each single stimulus and each series of ten on a 100-point NRS. We calculated the WUR as mean NRS for the five series of 10 divided by the mean NRS for the five single stimuli. We then log-converted this ratio, which served as a perceptual correlate of temporal pain summation.
- Vibration detection threshold (VDT): We determined VDT by applying a vibrating Rydell-Seiffer graduated tuning fork over the ulnar styloid process (hand), medial malleolus (foot) or temporal bone (face). We noted the value (range 0-8) at which the vibration was not felt anymore.
- Pressure-pain threshold (PPT): PPT was determined with a pressure algometer (models FPN50, FPN100, and FPN200, Wagner Instruments, USA) with a rubber tip and a probe area of 1 cm^2, range 0-2000 kPa. We applied increasing pressure on a muscle (thenar, abductor hallucis, or masseter) at an approximate rate of 50 kPa/s and noted the pressure corresponding to the subject's first pain sensation.
- Dynamic mechanical allodynia (ALL): Innocuous stimuli consisted of a standardized brush, cotton swab and cotton wad, each applied five times in a 1 second-stroke over the testing region. Numeric rating scale (NRS, range 0-100) for the pain sensation was noted. In healthy subjects, we stopped testing for ALL after 25 subjects because of absence of pain due to this test, as was to be expected.
- Thermal thresholds: Thermal tests consisted of cold and warmth detection thresholds (CDT and WDT), and the cold and heat pain thresholds (CPT and HPT). Stimuli were applied with a Pathway thermostimulator (Medoc, Israel). From a baseline temperature of 32°C, the temperature increased or decreased at a rate of 1°C/s until subjects noticed a change in temperature (CDT and WDT), until the first sensation of pain (CPT and HPT), or until the safety margin of 50°C or -10°C was reached. Each measurement was repeated three times. We calculated arithmetic means for CDT and WDT (expressed as the absolute difference from baseline of 32°C) and for the absolute CPT and HPT.

- Paradoxical heat sensations (PHS): The temperature sensory limen procedure consisted of alternating warm and cold stimuli, in which the number of PHS was noted (range 0-3).

Clinical and psychological characteristics

We collected the following data concerning symptoms and psychological characteristics from CUP patients:

- Pain location: Patients marked their pain locations on pain mannequins from the McGill Pain Questionnaire, Dutch Language Version (MPQ-DLV).[31,32] From these drawings, patients were classified as having 'chronic widespread pain (CWP)' or not according to criteria of the American College of Rheumatology.[33]
- Pain duration: Pain duration was recorded in the MPQ-DLV.
- Current pain intensity: We evaluated the current intensity of clinical pain symptoms on the testing day with a numeric rating scale (NRS) ranging from 0 to 100, with 0 signifying 'no pain' and 100 'worst pain imaginable'.
- Pain catastrophizing: We calculated the total score for pain catastrophizing on the Pain Catastrophizing Scale, Dutch Version (PCS).[34]
- Anxiety and depression: We calculated the total score on the Hospital Anxiety and Depression Scale (HADS), Dutch version,[35,36] as a compound measure for anxiety and depression.
- Somatization: We measured the tendency for somatization with the Symptoms Check List-90, somatization subscale (SCL-90-SOM),[37] Dutch version.
- Coping profile: Patients completed the Multidimensional Pain Inventory, Dutch language version (MPI-DLV).[38] We calculated the coping profile with available standard scoring software, on the basis of previously published factorial analysis. This resulted in a Dysfunctional, Interpersonally Distressed, Average, Adaptive or Anomalous subtype (or 'profile').[39]

Statistical analysis

Data pre-processing

For all QST tests except ALL, VDT, CPT and HPT, we log-converted values from individual subjects and calculated a geometric mean, since conversion to log-space has been shown to increase the normality of data;[24] we confirmed this increase in normality in our own data set before further analysis. Although we performed calculations in log-space, we also provide results in original space for easier interpretation. For VDT, CPT and HPT, we used unconverted data. For

WUR and ALL, we added 0.1 to all individual values prior to log-transformation to avoid a loss of zero rating values, in accordance with the DFNS protocol. However, data for ALL were still not normally distributed in either standard space or log-space (due to many 0 values, especially in healthy controls) and were thus analyzed with non-parametric tests.

Primary analysis

To study differences in QST-measures between patients and healthy controls, we needed to account for the fact that QST outcomes in this protocol have been shown to be dependent on age, body region and (for pain thresholds) on gender.[25,40] To this end, we first calculated means and standard deviations for healthy controls for each QST-test. We calculated these study-specific reference values separately for each body region, age group (18-39; 40 and higher) and gender, resulting in 12 reference values per test. We then converted all the individual patient data for each QST-test to study-specific Z-scores according to the formula:

$$\text{Z-score} = \text{Mean}_{\text{individual patient}} - \text{Mean}_{\text{healthy control group}} \,/\, \text{Standard deviation}_{\text{healthy control group}}$$

In this formula, high (above-zero) scores represent high sensitivity for painful and non-painful stimuli, and low scores represent low sensitivity. Testing for significant between-group differences consisted of a one-sample T-test on the patients' Z-scores with the null hypothesis of $\text{Mean}_Z=0$ and $\text{SD}_Z=1$.

To certify that the results from Z-value-analysis are valid, we performed a second (confirmatory) analysis of the primary research question by means of univariate general linear modelling (GLM). For each QST-test, we created a GLM with age (dichotomized), gender, testing region and group (patient or control) as the independent variables and the QST measure (not converted to Z-values) as the outcome variable. Most healthy subjects were tested in two body regions; for the GLM, we considered the data from the two body regions as separate cases. We included ALL in the GLM analysis despite the non-parametric characteristics of the data, since GLM analysis is robust for deviations from normality, especially in large samples.

Secondary analysis

A pre-planned secondary analysis focused on the relationship between putative risk factors for CUP and QST-data. This analysis was restricted to the CUP patients and consisted of separate ANCOVA models for each QST-test, with the different clinical and psychological measures (listed above) as independent variables and the Z-converted QST-values as outcome measures. Since the Z-scores are already normalized and corrected for differences in QST-data between genders, age groups and testing region, any effects we found may be considered as specific effects of the variable in question on QST-outcomes in CUP. We did not include ALL in this analysis because

of the non-parametric characteristics of this variable.

We separately studied the relationship between the NRS for current intensity of clinical pain and the QST-outcomes (simple linear regression).

To avoid type-I-error (false-positive results) in the abovementioned (primary, confirmatory and secondary) analyses with 11 outcome measures (QST-tests), we applied a Bonferroni correction for multiple tests; this led to a corrected p-value of 0.05/11 = 0.0045. Since the Bonferroni correction is considered conservative, its use may lead to increased type-II-error (false-negative results), especially in the case of correlated outcome measures. For this reason, we separately flagged results with p-values between 0.05 (uncorrected p-threshold) and 0.0045 (Bonferroni-corrected p-threshold).

Factor analysis

As an exploratory post-hoc analysis, we studied sources of common variance in the QST outcomes by means of principle axis factoring. This method seeks the least number of factors which can account for the common variance of a set of variables. For this analysis, we used the Z-converted data from all QST measures as variables except ALL, which we excluded because of non-linearity of results. From this analysis, we selected relevant factors based on the Kaiser criterion (minimum eigenfactor of 1) and the scree test (based on the slope of the plot of eigenvalues).

All analyses were performed in SPSS 19.0.0 (IBM, USA).

RESULTS

Patient inclusion and baseline characteristics

Of 105 patients who met inclusion criteria during the inclusion period, 20 patients did not participate (patient refusal: n=7; no time: n=4; physically unable to come: n=3; other reasons: n=6), leaving 85 CUP patients that were included for QST testing. The patients' and controls' characteristics are given in table 6.1.

Forty-four (52%) of patients had taken analgesic medication in the 24 hours preceding QST testing. Based on pain drawings, 38 patients (45%) met the criteria for CWP. We tested the following clinically painful regions in patients: hand (58%), foot (24%) and face (16%).

The healthy control group consisted of 90 persons; one subject was excluded after QST-testing because his data consisted of outliers on many tests (>2 SD below or above mean for healthy controls) and his verbal responses were inconsistent during testing. For another healthy subject, the PPT in the face area was excluded from further analysis because the subject expressed fear for facial pressure and consequently had very low (outlier) values for PPT; we

Table 6.1 Baseline characteristics of patients and controls

Characteristic	CUP patients	Healthy controls
N	85	89*
Gender, % females	68%	57%
Age in years, mean (SD)	49.1 (13.7)	37.0 (14.3)
NRS for clinical pain on testing day, mean (SD)	46.0 (27.5)	n/a
Pain duration in months, median (IQR)	60 (23–132)	n/a
Pain catastrophizing scale score, median (IQR)	20 (12-27.5)	n/a
Hospital Anxiety and Depression scale score, median (IQR)	10 (7-17.8)	n/a
SCL-90-somatization scale score, median (IQR)	29 (23-35)	n/a

* = number of healthy controls after exclusion of one outlier. IQR = interquartile range; NRS = numeric rating scale; SD = standard deviation.

did include her other QST-results in the analysis. In the final control group (n=89), we tested only 1 body region in 4 subjects due to time limits and 2 regions in all other subjects (total of 174 regional QST profiles).

QST: patients versus controls

For the healthy subjects, we calculated the mean values and standard deviations (log-converted, where appropriate) for each QST-test and each category.

We then calculated Z-values based on these healthy control data (table 6.2 and figure 6.1). A one-sample t-test for Z-scores confirmed a significant increase in pain sensitivity (corresponding to Z-scores that significantly exceed 0) in CUP patients compared to healthy control (reference) values for PPT, CPT and HPT ($p<0.0045$). Also, WUR was higher in CUP patients than in controls at the less conservative p-threshold ($p=0.035$). Detection threshold sensitivity was lower in CUP patients than in healthy controls (meaning that patients had higher thresholds) for CDT and WDT. NRS ratings for the ALL test were higher in patients than in controls ($p<0.001$ for all three body regions tested on a Mann-Whitney U test).

We then performed confirmatory GLM analysis for each of the QST-tests (table 6.3). This analysis supports the findings from the Z-score analysis, showing a group effect on PPT, CDT, WDT ($p<0.0045$), which turned out to be independent of body region, age, or gender. When considering a less conservative p-threshold of $p<0.05$, we also found a group effect for WUR, CPT, HPT and ALL. In contrast with the Z-score analysis, the GLM analysis showed an independent association of CUP with a higher number of PHS ($p=0.049$).

Table 6.2 QST results for CUP patients, expressed as Z-scores. Two-tailed p-values for the one-sample Student's t-test (null hypothesis Z=0, standard deviation=1). Positive scores represent high sensitivity for painful and non-painful stimuli, and negative scores represent low sensitivity. Dynamic mechanical allodynia (ALL) data are not included in this analysis since data are not normally distributed (see text).

QST-test	Mean Z (95%-CI)	p-value
Mechanical detection threshold (MDT)	-0.225 (-0.569 - 0.119)	0.197
Mechanical pain threshold (MPT)	0.123 (-0.208 - 0.454)	0.461
Wind-up ratio (WUR)	0.505 (0.037 - 0.974)	0.035[b]
Vibration detection threshold (VDT)	0.060 (-0.233 - 0.352)	0.686
Pressure pain threshold (PPT)	0.741 (0.349 - 1.134)	<0.001[a]
Cold detection threshold (CDT)	-1.290 (-1.642 - -0.937)	<0.001 [a]
Warmth detection threshold (WDT)	-0.663 (-0.979 - -0.346)	<0.001 [a]
Cold pain threshold (CPT)	0.631 (0.340 - 0.921)	<0.001 [a]
Heat pain threshold (HPT)	0.718 (0.403 - 1.033)	<0.001 [a]
Paradoxical heat sensations (PHS)	-1.032 (-2.170 - 0.106)	0.075

[a] p<0.0045 (significant at 0.05-level after Bonferroni correction); [b] p between 0.0045 and 0.05. 95%-CI = 95%-confidence interval.

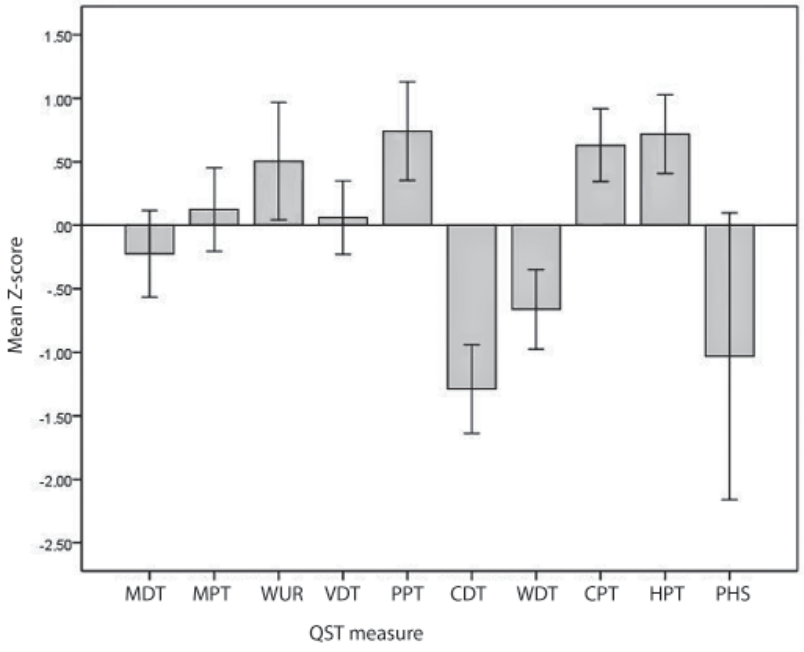

Figure 6.1 Bar chart of mean Z-scores (normalized QST-scores on the basis of data from the control group) for the CUP patients on the QST-tests. Error bars represent 95%-confidence intervals.

Table 6.3 Summary of confirmatory general linear model (GLM) analysis for the comparison of QST-outcomes in CUP patients and healthy control subjects (signified as the 'group' factor). Significant factors (main effects and interactions) that involve the group-factor are printed in bold. The main effects of the group-factor are specifically given in the two right-sided columns.

QST-test	Significant factors and first-order interactions in GLM (excluding intercept)	F-value for 'group' (df)	p-value for 'group'
MDT	age; gender; testing region	1.71 (1;231)	0.193
MPT	-	0.58 (1;228)	0.446
WUR	testing region; **group**; **testing region*group**	14.01 (1;207)	0.046[b]
VDT	age; testing region; age*testing region	0.04 (1;230)	0.838
PPT	gender; testing region; **group**	8.28 (1;226)	0.004[a]
CDT	age; testing region; **group**; age*gender	48.288 (1;227)	<0.001[a]
WDT	age; gender; testing region; **group**; **testing region*group**	12.67 (1;226)	<0.001[a]
CPT	age; **group**	7.51 (1;227)	0.007[b]
HPT	age; gender; **group**	4.81 (1;225)	0.029[b]
PHS	testing region; **group**; **gender*group**	3.90 (1;237)	0.049[b]
ALL	**group**	7.94 (1;154)	0.005[b]

[a] $p<0.0045$ (significant at 0.05-level after Bonferroni correction); [b] p between 0.0045 and 0.05; df = degrees of freedom; we refer to table 6.2 for the meaning of the abbreviations for QST-tests.

Association of QST with risk factors for CUP

We subsequently performed ANCOVA analyses *within* the CUP group for associations of demographic, pain-related, and psychological factors with the Z-scores for the QST-tests as the outcome variable (table 6.4).

The following associations were significant after Bonferroni correction:

- Presence of CWP was associated with higher sensitivity on the VDT (higher VDT);
- We found an interaction between gender and presence of widespread pain on PPT: for both genders, patients with CWP had higher PPT sensitivity than patients without CWP, but this association was stronger for males than for females;
- Patients with CWP had a higher number of PHS than patients without CWP;
- Number of PHS differed between coping profiles, with the most PHS for the average profile and the least PHS for the anomalous profile. The coping profiles were also associated with Z-scores for several other modalities (PPT, WDT, HPT) at a less conservative p-threshold (p between 0.0045 and 0.05).

Table 6.4 Relationship of risk factors for CUP and QST outcomes within the CUP patients; summary of analysis of covariance. Dynamic mechanical allodynia (ALL) data are not included in this analysis since data are not normally distributed (see text).

QST-test	Age	Gender	Presence of CWP	Duration of symptoms	Depression/ anxiety (total HADS score)	Somatization (SCL90)	Catastrophizing (total PCS score)	Coping profile (from MPI)	First-order interaction effects
MDT	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	CWP * coping cluster (p=0.013[b], in CWP-patients: highest sensitivity in interpersonally distressed patients; in non-CWP-patients: lowest sensitivity in interpersonally distressed patients)
MPT	n.s.	n.s.	n.s.	p=0.008[b] (Long duration ~ high sensitiity)	n.s.	n.s.	p=0.027[b] (High PCS ~ low sensitivity)	n.s.	Gender * CWP (p=0.047[b], CWP ~ lower sensitivity in males; CWP ~ higher sensitivity in females)
WUR	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
VDT	p=0.005[b] (high age ~ high sensitivity	n.s.	p=0.004[a] (CWP ~ high sensitivity)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
PPT	n.s.	n.s.	p=0.037[b] (CWP ~ low sensitivity)	n.s.	n.s.	n.s.	n.s.	p=0.011[b] (sensitivity highest for dysfunctional, lowest for anomalous)	Gender * CWP (p=0.003[a], larger effect of CWP in males than in females)
CDT	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Table 6.4 continues on next page

Table 6.4 *continued from previous page*

QST-test	Age	Gender	Presence of CWP	Duration of symptoms	Depression/ anxiety (total HADS score)	Somatization (SCL90)	Catastrophizing (total PCS score)	Coping profile (from MPI)	First-order interaction effects
WDT	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	p=0.031[b] (sensitivity for highest for adaptive, lowest for anomalous)	n.s.
CPT	n.s.	n.s.	n.s.	n.s.	p=0.022[b] (high HADS ~ low sensitivity)	n.s.	n.s.	n.s.	n.s.
HPT	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	p=0.005[b] (sensitivity highest for dysfunctional, lowest for anomalous)	Gender * CWP (p=0.011[b], effect unclear)
PHS	n.s.	p=0.025[b] (Higher number of PHS in males)	p=0.001[a] (Higher number of PHS when CWP is present)	n.s.	n.s.	n.s.	n.s.	p=0.003[a] (highest PHS (=lowest sensitivity) in average, lowest PHS in anomalous)	Gender * CWP (p=0.005[b], effect of CWP larger in males than in females) Gender * coping cluster (p<0.001[a], effect of coping cluster larger in males than in females) CWP * coping cluster (p=0.001[a], in CWP-patients: lowest sensitivity in 'average' profile; in non-CWP-patients: highest sensitivity in 'average' profile)

[a] p<0.0045 (significant at 0.05-level after Bonferroni correction).; [b] p between 0.0045 and 0.05. CWP = chronic, widespread pain; df = degrees of freedom; n.s. = test not significant; we refer to table 6.1 for the meaning of the abbreviations of QST-tests.

- We found a complex interaction between gender, presence of CWP, and coping profile on the number of PHS (see table 6.4 for details). These three variables were also involved in interactions for MDT, MPT, PPT and HPT at the less conservative p-threshold (p between 0.0045 and 0.05).

We found no significant relationship between clinical pain ratings (NRS) on the day of QST testing and any of the QST-outcomes (p>0.1 for all tests).

Factor analysis

We found four factors with an eigenvalue of 1 or more (table 6.5). From a scree plot (figure 6.2) we concluded that the first two factors were most important with a combined explained variance of 45% whereas the third and fourth factors were probably redundant with an additional combined explained variance of 23% and low factor loadings. Factor 1 was primarily based on pain and detection thresholds for temperature as well as on PPT and (to a lesser extent) MPT. Factor 2 was primarily based on WDT, WUR and (to a lesser extent) CDT. Moreover, this factor loaded negatively on all pain thresholds, most notably on MPT, except for HPT.

Table 6.5 Results from the factor analysis; only factors with an eigenvalue of 1 or more are noted. Factor loadings >0.3 are printed in bold.

		Factor 1	Factor 2	Factor 3	Factor 4
Eigenvalue (% of variance)		2.913 (29%)	1.626 (16%)	1.244 (12%)	1.106 (11%)
Variable (QST-test) loadings	MDT	-0.142	0.246	**0.369**	**0.344**
	MPT	**0.345**	**-0.572**	-0.187	**0.382**
	WUR	0.037	**0.453**	**0.326**	0.152
	VDT	-0.071	0.084	-0.104	0.262
	PPT	**0.755**	-0.226	-0.030	0.003
	CDT	**0.535**	**0.318**	-0.202	-0.171
	WDT	**0.660**	**0.574**	-0.240	0.073
	CPT	**0.745**	-0.262	0.401	-0.085
	HPT	**0.758**	0.038	0.141	0.025
	PHS	0.067	0.147	-0.284	0.224

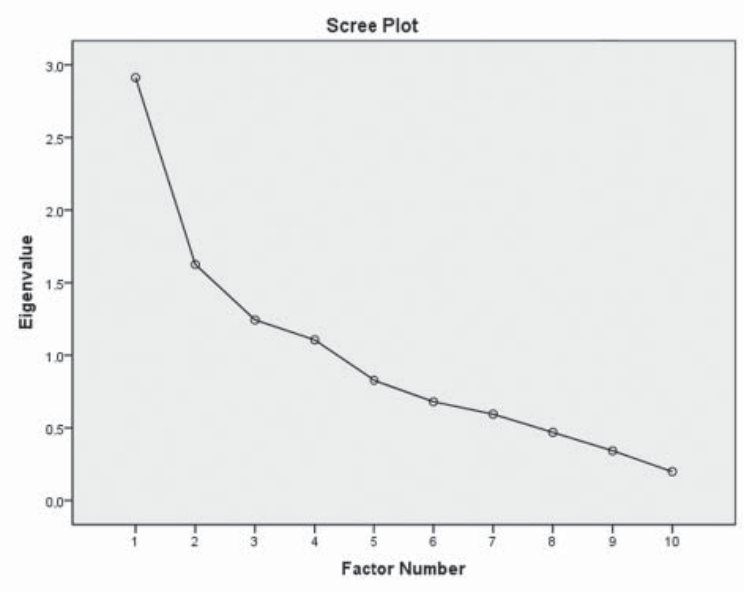

Figure 6.2 Scree plot from factor analysis, aimed at identifying underlying patters of common variance in QST outcome measures.

DISCUSSION

In this QST study, we found that chronic, unexplained pain is associated with increased sensitivity for pain from different modalities (pressure, heat, cold), as well as hyposensitivity for (non-painful) detection thresholds for temperature. We also found evidence for an increase of temporal summation in CUP. QST findings are only associated with psychological and demographic parameters to a limited extent in CUP patients. Exploratory factor analysis reveals an underlying pattern of variance in the QST data that is mostly based on two factors: a pain- and temperature-based factor which is suggestive of a dysfunction in the small-fiber based sensory modalities, and a factor based on temperature detection and wind-up ratio.

The sensory profile of CUP

The combination of hyperalgesia across modalities, increased temporal summation of pain (wind-up) and hypoesthesia for temperature is a new finding in CUP. The increase in WUR was not significant in the primary analysis after correction for multiple testing, but the replication of this finding in the confirmatory analysis and the high factor loadings for WUR in the factor analysis supports that an increased WUR is a true-positive finding.

In line with our current findings, several previous studies have reported on increased pain sensitivity in CUP syndromes. Increased sensitivity for cold and heat pain,[26,27] as well as increased WUR were found in fibromyalgia.[41] Hyperalgesia for pressure and temperature pain in whiplash-associated pain symptoms was associated with poor outcome.[28] Recently, a large-scale study reported hyperalgesia to pressure pain and (to a lesser extent) mechanical and temperature pain in temporomandibular disorder (TMD).[13]

Previous studies that directly compared different CUP syndromes point towards an overlap in pain sensitivity for these syndromes. Patients with chronic low back pain and fibromyalgia both have higher pressure pain sensitivity than controls.[42] Pfau et al. compared QST profiles (as assessed with the DFNS protocol) in patients with TMD, fibromyalgia patients, and healthy controls and found increased pain sensitivity for both patient groups across modalities (for cold, pressure, pinprick, but not for heat) as well as a decreased sensitivity to mechanical stimuli (MDT) in TMD and in fibromyalgia;[16] both the hyperalgesia and the hyposensitivity for mechanical stimuli were more extreme in fibromyalgia than in TMD. They further reported that a subgroup of TMD patients exhibited a widespread pattern of pressure pain hypersensitivity comparable to fibromyalgia patients, which was found to be independent of psychological parameters. Sensory profiles in patients with idiopathic leg pain of a pseudoradicular pattern were characterized by hypoesthesia to several non-painful modalities, but no abnormalities in pain sensitivity were reported.[43]

Although these previous reports and our findings vary somewhat in the exact modalities in which abnormalities occur, a common pattern may be identified of (a) across-modality hyperalgesia; and (b) a certain degree of hyposensitivity to non-painful stimuli, although the latter finding is not found consistently.[26,27] Of note, we did not perform a subgroup analysis for differences between the CUP syndromes ('functional pain syndromes') in our study since the patients in our cohort were not systematically evaluated for the presence of (criteria for) such a syndrome.

The combination of increased temperature detection thresholds (hyposensitivity) and hyperalgesia for different painful modalities might argue for small fiber dysfunction in CUP. In our factor analysis, the 'small fiber function' factor explained 26% of the total variance. However, pressure hyperalgesia and increased WUR are not typical for small fiber neuropathies.[44] Also, the sensory profile we found is not consistent with those found in different neuropathic pain conditions.[23] The finding of across-modality hypersensitivity to pain and (at a less conservative p-threshold) increased temporal summation of pain is better compatible with a central (supraspinal) cause than of a local cause. Specifically, the finding of increased temporal summation of pain (increased WUR) may serve as a marker of central sensitization in CUP for therapeutic research.[45] It is not directly clear how the finding of hypoesthesia to thermal non-painful stimuli fits into this theoretical framework. Speculatively, increased attentional bias

towards painful stimuli (resulting in hyperalgesia)[46] may be compensated by decreased attention towards stimuli that are clearly not painful (hyposensitivity for non-painful stimulus detection).

The relation of QST findings with clinical and psychological factors

A previous study in fibromyalgia patients aimed to identify subgroups of patients based on pressure pain sensitivity and psychological factors (depression, catastrophizing, control over pain). The authors found subgroups with either (a) low PPT tenderness and moderate psychological abnormalities; (b) high PPT tenderness and low psychological abnormalities; (c) high PPT tenderness and high psychological abnormalities. This suggestion of – more or less – mutually exclusive 'psychological' and 'hyperalgesic' CUP subgroups is generally not supported by the relationships between QST measures and psychological characteristics in our data. Altogether, we found only a limited number of associations between psychological measures and QST outcomes, which is compatible with the notion (supported by previous findings)[28] that intrinsic pain sensitivity has a role in the pathophysiology of CUP that is largely independent of clinical and psychological risk factors.

Strengths, limitations and future studies

In this relatively large study of CUP, we applied a standardized QST protocol that included the most relevant sensory modalities and tests. Comparison with a control group and the use of several analytical techniques that show converging results add to the validity of our findings.

We chose to study CUP as a group rather than investigating syndrome-defined subgroups, since these syndromes may be considered to form a spectrum rather than representing separate diseases.[11] One limitation of our study is that we cannot investigate possible differences in sensory profiles between CUP syndromes (functional pain syndromes) since we could not obtain detailed information on these syndromes in our patients. However, rather than focusing on the imperfect criteria for different syndromes as a basis for patient classification, our findings may serve as a basis for mechanism-based classification in CUP, e.g. in high versus low pain amplifiers. Previous reports suggest that such 'sensory phenotyping' of chronic pain patients is of value in determining their prognosis and in the prediction of the treatment effect.[47,48] Whether QST measures, individually or as a group, indeed have such a prognostic and predictive value in CUP should be studied in longitudinal studies that incorporate clinical, psychological and QST measures.

Many patients in our study used analgesic drugs which they were allowed to continue on the day of QST testing for practical and ethical reasons. We cannot exclude the possibility that the use of medication influenced our results.

Conclusion

The sensory profile of chronic, unexplained pain (CUP) is characterized by increased pain sensitivity for heat, cold, and pressure, increased temporal summation of pain, and hyposensitivity for non-painful temperature stimuli. These findings are only partially correlated to clinical and psychological risk factors of chronic pain. The sensory profile may serve as an easily evaluable marker of dysfunctional CNS processing of pain; its clinical value in CUP remains to be determined.

ACKNOWLEDGEMENTS

The authors wish to thank K. Schöls for assistance in acquisition of QST data and L.L. Teunissen, A.L. Liem, J.W.G. Jacobs and all physicians in the participating centers for assistance in patient inclusion.

REFERENCES

1. Bjordal JM, Klovning A, Ljunggren AE, Slordal L. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomised placebo-controlled trials. Eur J Pain 2007;11:125-38.
2. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain 2010;150:573-81.
3. Woolf CJ, Bennett GJ, Doherty M, Dubner R, Kidd B, Koltzenburg M, et al. Towards a mechanism-based classification of pain? Pain 1998;77:227-9.
4. Maiden NL, Hurst NP, Lochhead A, Carson AJ, Sharpe M. Medically unexplained symptoms in patients referred to a specialist rheumatology service: prevalence and associations. Rheumatology 2003;42:108-12.
5. Snijders TJ, de Leeuw FE, Klumpers UMH, Kappelle LJ, van Gijn J. Prevalence and predictors of unexplained neurological symptoms in an academic neurology outpatient clinic - An observational study. J Neurol 2004;251:66-71.
6. Lame IE, Peters ML, Vlaeyen JW, Kleef M, Patijn J. Quality of life in chronic pain is more associated with beliefs about pain, than with pain intensity. Eur J Pain 2005;9:15-24.
7. Aaron LA, Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. Ann Intern Med 2001;134:868-81.
8. Koleck M, Mazaux JM, Rascle N, Bruchon-Schweitzer M. Psycho-social factors and coping strategies as predictors of chronic evolution and quality of life in patients with low back pain: a prospective study. Eur J Pain 2006;10:1-11.
9. Petrak F, Hardt J, Kappis B, Nickel R, Egle UT. Determinants of health-related quality of life in patients with persistent somatoform pain disorder. European Journal of Pain 2003;7:463-71.

10. Mayer EA, Bushnell MC. Functional Pain Syndromes: Presentation and Pathophysiology. Seattle, WA: IASP press; 2009.

11. Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? Lancet 1999;354:936-9.

12. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011;152:S2-15.

13. Greenspan JD, Slade GD, Bair E, Dubner R, Fillingim RB, Ohrbach R, et al. Pain sensitivity risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case control study. J Pain 2011;12:T61-T74.

14. McDermid AJ, Rollman GB, McCain GA. Generalized hypervigilance in fibromyalgia: evidence of perceptual amplification. Pain 1996;66:133-44.

15. Fernandez-de-Las-Penas C, Galan-Del-Rio F, Fernandez-Carnero J, Pesquera J, rendt-Nielsen L, Svensson P. Bilateral widespread mechanical pain sensitivity in women with myofascial temporomandibular disorder: evidence of impairment in central nociceptive processing. J Pain 2009;10:1170-8.

16. Pfau DB, Rolke R, Nickel R, Treede RD, Daublaender M. Somatosensory profiles in subgroups of patients with myogenic temporomandibular disorders and Fibromyalgia Syndrome. Pain 2009;147:72-83.

17. Henningsen P, Zipfel S, Herzog W. Management of functional somatic syndromes. Lancet 2007;369:946-55.

18. Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, et al. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain 2004;127:835-43.

19. Jensen KB, Kosek E, Petzke F, Carville S, Fransson P, Marcus H, et al. Evidence of dysfunctional pain inhibition in Fibromyalgia reflected in rACC during provoked pain. Pain 2009;144:95-100.

20. Smith BH, Macfarlane GJ, Torrance N. Epidemiology of chronic pain, from the laboratory to the bus stop: time to add understanding of biological mechanisms to the study of risk factors in population-based research? Pain 2007;127:5-10.

21. Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. J Pain 2009;10:556-72.

22. Shy ME, Frohman EM, So YT, Arezzo JC, Cornblath DR, Giuliani MJ, et al. Quantitative sensory testing: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2003;60:898-904.

23. Maier C, Baron R, Tolle TR, Binder A, Birbaumer N, Birklein F, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. Pain 2010;150:439-50.

24. Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain 2006;10:77-88.

25. Rolke R, Baron R, Maier C, Tolle TR, Treede RD, Beyer A, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 2006;123:231-43.

26. Desmeules JA, Cedraschi C, Rapiti E, Baumgartner E, Finckh A, Cohen P, et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. Arthritis Rheum 2003;48:1420-9.

27. Hurtig IM, Raak RI, Kendall SA, Gerdle B, Wahren LK. Quantitative sensory testing in fibromyalgia patients and in healthy subjects: identification of subgroups. Clin J Pain 2001;17:316-22.

28. Sterling M, Jull G, Vicenzino B, Kenardy J. Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery. Pain 2003;104:509-17.

29. Hollins M, Harper D, Gallagher S, Owings EW, Lim PF, Miller V, et al. Perceived intensity and unpleasantness of cutaneous and auditory stimuli: an evaluation of the generalized hypervigilance hypothesis. Pain 2009;141:215-21.

30. Peters ML, Vlaeyen JW, van Drunen C. Do fibromyalgia patients display hypervigilance for innocuous somatosensory stimuli? Application of a body scanning reaction time paradigm. Pain 2000;86:283-92.

31. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1:277-99.

32. Verkes RJ, Vanderiet K, Vertommen H, Van der Kloot WA, Van der Meij J. De MPQ-DLV: een standaard nederlandstalige versie van de McGill Pain Questionnaire voor België en Nederland. In: Kloot WA van der, Vertommen H, editors. De MPQ-DLV. Een standaard nederlandstalige versie van de McGill Pain Questionnaire. Achtergronden en inleiding.Lisse: Swets & Zeitlinger BV; 1989. p. 57-74.

33. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160-72.

34. Crombez G, Vlaeyen JW, Heuts PH, Lysens R. Pain-related fear is more disabling than pain itself: evidence on the role of pain-related fear in chronic back pain disability. Pain 1999;80:329-39.

35. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997;27:363-70.

36. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.

37. Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale--preliminary report. Psychopharmacol Bull 1973;9:13-28.

38. Lousberg R, Van Breukelen G.J., Groenman NH, Schmidt AJ, Arntz A, Winter FA. Psychometric properties of the Multidimensional Pain Inventory, Dutch language version (MPI-DLV). Behav Res Ther 1999;37:167-82.

39. Turk DC, Rudy TE. Toward an empirically derived taxonomy of chronic pain patients: integration of psychological assessment data. J Consult Clin Psychol 1988;56:233-8.

40. Magerl W, Krumova EK, Baron R, Tolle T, Treede RD, Maier C. Reference data for quantitative sensory testing (QST): refined stratification for age and a novel method for statistical comparison of group data. Pain 2010;151:598-605.

41. Klauenberg S, Maier C, Assion HJ, Hoffmann A, Krumova EK, Magerl W, et al. Depression and changed pain perception: hints for a central disinhibition mechanism. Pain 2008;140:332-43.

42. Giesecke T, Gracely RH, Grant MA, Nachemson A, Petzke F, Williams DA, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis Rheum 2004;50:613-23.

43. Freynhagen R, Rolke R, Baron R, Tolle TR, Rutjes AK, Schu S, et al. Pseudoradicular and radicular low-back pain--a disease continuum rather than different entities? Answers from quantitative sensory testing. Pain 2008;135:65-74.

44. Bachmann CG, Rolke R, Scheidt U, Stadelmann C, Sommer M, Pavlakovic G, et al. Thermal hypoaesthesia differentiates secondary restless legs syndrome associated with small fibre neuropathy from primary restless legs syndrome. Brain 2010;133:762-70.

45. Nijs J, Meeus M, Van OJ, Roussel N, De KM, Ickmans K, et al. Treatment of central sensitization in patients with 'unexplained' chronic pain: what options do we have? Expert Opin Pharmacother 2011;12:1087-98.

46. Snijders TJ, Ramsey NF, Koerselman F, van Gijn J. Attentional modulation fails to attenuate the subjective pain experience in chronic, unexplained pain. Eur J Pain 2010;14:282-10.

47. Jull G, Sterling M, Kenardy J, Beller E. Does the presence of sensory hypersensitivity influence outcomes of physical rehabilitation for chronic whiplash?--A preliminary RCT. Pain 2007;129:28-34.

48. Sterling M, Jull G, Kenardy J. Physical and psychological factors maintain long-term predictive capacity post-whiplash injury. Pain 2006;122:102-8.

7

Attentional modulation fails to attenuate the subjective pain experience in chronic, unexplained pain

Tom J. Snijders
Nick F. Ramsey
Frank Koerselman
Jan van Gijn

Eur J Pain 2010;14:282.e1-e10

ABSTRACT

Background: Chronic, unexplained pain is a common, ill-understood clinical problem. Increased sensitivity for pain and other stimuli is often implied as an underlying mechanism. Attentional processes influence central pain processing and might mediate hypersensitivity at a cerebral level.

Aims: To study patients with chronic, unexplained pain with respect to (a) subjective pain experience; (b) effects of attentional manipulation; (c) level at which alterations in pain processing occur: locally (symptomatic body region), or generalized.

Methods: We compared 16 patients with chronic, unexplained limb pain with 16 matched healthy controls. Pain thresholds to electrical stimuli were recorded. Subjects then received individually thresholded painful and non-painful stimuli, with manipulation of attention towards or away from pain. The intensity of pain perception was recorded by means of visual analogue scales (VAS). Pain thresholds and effects of Attention and Laterality on VAS scores were compared between groups by means of general linear modeling (restricted to 12 patients with unilateral pain and 12 controls).

Results: Distraction increased thresholds for pain in healthy volunteers, but this effect was significantly attenuated in patients. Significant interactions between attention-effects, stimulus laterality and stimulus intensity indicated that VAS scores for painful stimuli were attenuated during distraction in healthy controls, but not in pain patients.

Conclusions: Results support the notion that pain processing is enhanced in chronic, unexplained pain, and that the influence of attentional modulation on pain processing is attenuated. Potential cerebral mechanisms are changes in either attentional allocation or attention-mediated descending pain modulation. The changes seem to occur at a generalized level.

INTRODUCTION

In many chronic pain patients, no identifiable disease or pathologic process can be identified as the cause of their pain. The origin of pain is by definition unknown in somatoform pain disorder,[1] and in many cases of chronic widespread pain. Chronic, unexplained pain is also a key feature in functional-somatic syndromes such as fibromyalgia or irritable bowel syndrome. Its prevalence is hard to determine, but the problem is common in several medical settings.[2,3]

Although chronic, unexplained pain affects a broad variety of patients, the existence of common features (e.g. symptomatology, tendency to catastrophize) lends support to the view of these syndromes as a spectrum rather than as separate entities.[4]

Several findings suggest an important role of supraspinal mechanisms in chronic, unexplained pain: (a) symptoms are often widespread; (b) several pain syndromes are associated with higher order cognitive processing such as catastrophizing;[5] (c) neuroimaging reveals abnormal cerebral pain processing in fibromyalgia and somatoform pain disorder.[6,7]

As a consequence, the interaction of pain processing and attention might be of special interest in these patients. Distraction causes lower pain ratings to acute, experimental pain in healthy subjects, with a more demanding distraction task causing greater pain attenuation.[8] These findings have been contradicted;[9] at higher intensities and longer pain duration, the effect of distraction diminishes or even reverses.[10,11]

In chronic pain, attention-related pain processing is disturbed. On a cold pressor task, focused attention induced a stronger pain-enhancing effect in chronic back pain patients than in controls.[11] Increased attention for somatosensory stimuli is a cardinal feature of the generalized hypervigilance theory, in the sense that attentional bias towards pain and other physical sensations would cause a generalized (supraspinal) enhancement of pain experience.[12,13] The generalized hypervigilance theory is supported by the finding of lower thresholds for painful stimuli,[14] as well as for acoustic stimuli.[12] In this theory, pain and pain-related stimuli prevail over other information, and thus studies are preferably performed in situations of competing attentional demands.[15,16] In discordance with generalized hypervigilance, a study on fibromyalgia did not demonstrate hypervigilance to innocuous stimuli (presented alone or during divided attention).[17]

In the light of these previous findings, we aimed to study two aspects of chronic, unexplained pain: (a) the effect of attention on pain processing and (b) the extent of altered processing: be it localized to the body region of pain symptoms, or generalized. To test the hypothesis of a generalized attention-dependent alteration in pain processing in chronic, unexplained pain, we performed a psychophysical study in patients and healthy controls, assessing the effect of attentional manipulation on the subjective pain experience in painful and asymptomatic body regions.

MATERIALS AND METHODS

Participants

Patients were recruited from the neurology outpatient clinic of the University Medical Center Utrecht, at the visit (first consultation or follow-up visit) where the diagnosis of unexplained pain was established and communicated by their physician. Full inclusion and exclusion criteria are listed in supplemental table S7.1. For an evaluation of the possible cause of pain symptoms, all patients underwent history taking and physical examination by their treating physician, either a neurologist or an experienced resident of neurology. Ancillary investigations, such as electromyography or neuroimaging studies, were performed at the discretion of the treating physician. We did not include patients with well-defined diseases or syndromes of poorly or incompletely known pathophysiology, such as neuralgic amyotrophy or migraine. Although the relation between pain symptoms and psychological factors is routinely addressed as a part of clinical work-up, an obvious relation of this kind was not mandatory for inclusion. Psychiatric co-morbidity did serve as ground for exclusion, especially mood and anxiety disorders, which are known to influence pain experience in a complex manner.[18-20]

Use of analgesic medication, including low-dose opioids, was not a reason for exclusion, because of ethical difficulties in tapering such drugs. Patients who regularly used benzodiazepines were excluded because of possible confounding attention-related effects of these drugs.[21] We did not exclude patients with medical co-morbidity, including conditions causing pain symptoms, as long as this condition did not sufficiently explain the pain symptoms in question.

Sixteen patients and 16 matched healthy control subjects completed the study (general linear model (GLM) analyses were restricted to the 12 patients with unilateral pain and their matched controls; see below). Six other patients did not complete the study after initial inclusion because of incomplete study components, insufficient understanding of oral and written Dutch or revision of their medical diagnosis. Patients' characteristics are summarized in supplemental table S7.2. The average age of patients was 47.5 years (range 23–68), with 11 (69%) females and five (31%) males. The median duration of patients' pain symptoms was 2.3 years (range 0.8– 45.0). The most frequently involved body region was the upper leg (with or without back pain). Four patients presented with symmetrically distributed pain; they (and their matched controls) did not undergo contralateral stimulation. Ten patients (63%) did not work (sick leave, not employed or part-time work) because of their pain symptoms.

We obtained detailed information about the patients' professional and social situation, as well as data on pain symptoms. For this last purpose, all patients completed two questionnaires, both in a validated Dutch translation: the McGill Pain Questionnaire (MPQ-DLV), evaluating the

patient's pain experience;[22,23] and the Multidimensional Pain Inventory (MPI-DV), measuring impact of pain on social interaction and daily living.[24,25]

Control subjects were healthy volunteers without major pain symptoms, relevant medical history or use of analgesics. Psychiatric morbidity was excluded using the MINI International Neuropsychiatric Interview (MINI Plus).[26] They were matched with patients for age, gender and handedness.

All subjects gave oral and written informed consent before the experiments. This study was approved by the medical ethics committee of the University Medical Center of Utrecht, The Netherlands in accordance with the Declaration of Helsinki 2008 (http://www.wma.net/e/policy/b3.htm (accessed 03.03.09.)).

General procedure

After inclusion, subjects were scheduled to visit our clinic at one or two occasions. After having given informed consent, they underwent the MINI International Neuropsychiatric Interview (MINI Plus) and completed the questionnaires,[26] and personal data were acquired. All subjects then underwent initial stimulation to get used to the type of stimulus, followed by threshold measurements for the attention modulation task, and bilateral pain thresholds, respectively, for approximately 45 min. This was followed by the actual experiment, with stimulation for approximately 30 min. The experimental procedure is depicted schematically in figure 7.1.

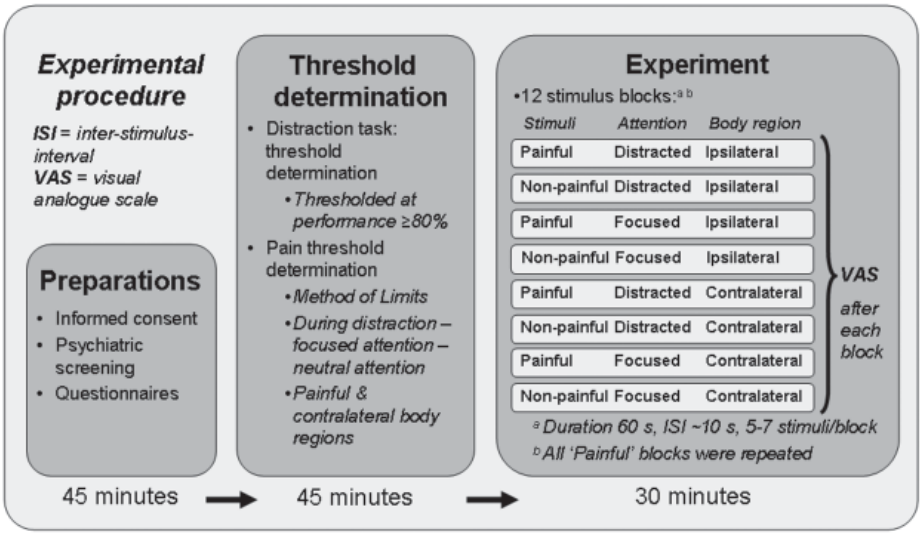

Figure 7.1 Experimental procedure, describing the different phases of the experiment including stimuli and attentional manipulation. The duration of each phase is stated in the bottom line.

Stimuli

All stimuli were applied with a transcutaneous electrical nerve stimulator (TENS)-device (Elpha 2000, Danmeter A/S, Odense C, Denmark). This device contained two stimulators, which could be alternately activated by means of a switch (in house production). Two standard electro-encephalography (EEG)-type electrodes were attached to the subject's skin at a distance of 4 cm. Before we placed the electrodes, the electrode site was prepared by removing the outer epidermal skin layer with abrasive skin prepping gel (Nuprep, Weaver & Co., Aurora CO, USA), and applying standard electrode gel. Stimuli consisted of short, pseudorandomized (0.5–1.0 s) pulse trains (frequency 10 Hz, pulsewidth 250 μs). The inter-stimulus interval randomly varied between 7 and 13 s. This inter-stimulus interval was chosen because an inter-stimulus interval of 10 s or more ensures a minimal dependence of stimulus perception on other stimuli, whereas shorter inter-stimulus intervals yield relatively higher perceived intensities of pain at stimulus intensities around the pain threshold.[27] The goal of varying both the stimulus duration and the inter-stimulus interval was to minimize anticipation and predictability of stimuli for subjects.[28] We presented stimuli in blocks of 60 s, containing 5–7 identical stimuli. The variation of the number of stimuli in each block was introduced for the purpose of the selective attention (stimulus counting) task. The 5–7 stimuli in each block were in all cases preceded by the same non-painful stimulus because we wished to minimize predictability of the next stimulus intensity.

Stimulus location was chosen according to the location of the pain reported by each individual patient, as recorded in the MPQ-DLV. In case of multifocal pain, we selected a site that was unilaterally involved. A location that was contralateral to the affected body part was selected for control stimulation. Healthy subjects received stimuli in the same region as their matched patient. Four patients had symmetrically distributed pain, making contralateral control stimulation impossible; in these patients (and in their matched control subjects), we performed only unilateral tests. After every electrode placement, we applied test stimuli to verify whether a sharp, pricking sensation was described, and to test for strong (and potentially distracting) local muscle contraction. In cases with other stimulus descriptions, or in cases of strong muscle contraction, the electrodes were moved within the clinical pain region (or the corresponding contralateral region).

Pain thresholds

Stimuli were applied at several intensities: painful and nonpainful stimuli (for a definition: see below). The non-painful stimuli were used to reduce predictability of painful stimulation, in order to minimize (augmenting) anticipation effects.[29-31] Furthermore, the application of non-painful stimuli makes it possible to distinguish specific pain-related responses from general responses to sensory information.

We obtained individual thresholds by means of a Method of Limits-type paradigm. In this paradigm, the applied stimulus intensity gradually increases from zero, until the subject labels the stimulus as painful. Next, the subject is stimulated with an intensity above the threshold, which gradually decreases until the subject does no longer consider the stimulus painful.[32] We performed both the gradual increase and the decrease using steps of 2 mA, followed by repetition using 1 mA-steps. This threshold measurement was repeated twice, at each body side and in three attentional states: neutral attention (continuously counting silently from 1 to 10), selective attention for pain and distraction from pain, yielding six different pain thresholds per subject (three for each body side; more information under the next section). To minimize habituation to, and predictability of stimuli, we used two painful and two non-painful stimulus intensities. The painful intensities were defined as 1 mA above the threshold in a state of neutral attention, and 1 mA above the highest of the three thresholds. The two nonpainful intensities were chosen as follows: 1 mA below the threshold with neutral attention, and 1 mA below the lowest of the three thresholds; for patients in whom the neutral attention- threshold was the lowest, the two non-painful stimulus types were of the same intensity. In statistical analysis, non-painful stimuli of both intensities were collapsed as were painful stimuli of both intensities. We used small differences in intensity between painful and non-painful stimuli in order to minimize reporting bias from an exaggerated response to obviously painful stimuli.

Attentional modulation

We manipulated the subjects' attentional states into either selective attention for pain or distraction from pain. Selective attention for pain entailed counting the number of applied stimuli in a certain period of time (a block). Distraction involved performing a divided attention task.[33] In this computerized version of an oddball paradigm, subjects see flashing dots of a certain diameter on screen, and hear tones of a certain frequency (referred to as non-targets), with varying interstimulus intervals (mean 1.0 s). Randomly, dots and tones of a slightly different diameter or frequency (called oddballs or targets) are presented within the series of non-targets. Subjects have to hit a button every time a target is presented. The magnitude of difference in diameter/frequency was separately determined in a session before the actual experiment with a threshold assessment procedure. This procedure measures the minimum difference in object diameter or sound frequency that still allows a subject to correctly detect 80% of the presented targets. This cut-off point represents the minimum difference that the subject can still properly identify, since performance tends to drop sharply with smaller differences. This is illustrated for four individual subjects in figure 7.2.

With this task, we aimed to achieve a high cognitive load of the distraction task, in order to obtain a maximum distraction-related effect on pain ratings.[8] We recorded the subjects'

performance on the divided attention task during the actual experiment; this performance served as a measure of the extent to which distraction was successful.

The subjects were informed in a general sense about the fact that we studied attention, but we did not tell them about the exact nature and goal of the attentional manipulation until the end of the study. In this way, we aimed to achieve passive (non-intentional) rather than active attentional manipulation.[34]

Design of actual experiment

The experiment was conducted with a 2 x 2 x 2 x 2 design, with effects of chronic unexplained pain as a between-subjects factor (factor 'Group': patients versus controls, see below) and 'Stimulus intensity' (painful versus non-painful), 'Laterality' (symptomatic versus non-symptomatic side) and 'Attention' (focused versus distracted) as within-subjects factors. The 'Laterality' factor was not tested in patients with symmetrically distributed pain or their matched control subjects. The three stimulus dimensions resulted in eight permutations of stimulus test conditions (four in cases with symmetrically distributed pain). We presented each condition in a block of 60 s, and blocks were presented in a pseudo- randomized order, while subjects were unaware of the stimulus type. Each block of painful stimuli was presented twice, and blocks of non-painful stimuli were presented once. This resulted in a total of 12 blocks (six in cases with symmetrically distributed pain). After each block, subjects rated the perceived intensity of the stimuli in that block on a visual analogue scale (VAS), with a range from 0 mm (no pain at all) to 100 mm (worst pain imaginable). Subjects received standardized instructions on how to use the VAS.[35]

Analysis

Pain threshold determination data were analyzed with GLM for repeated measures in 12 subjects per group, with 'Group' as between-subjects factor, and 'Attention' and 'Laterality' as within subject factors.

For the actual experiment, the VAS scores were analyzed with GLM for repeated measures, with 'Group' as between-subjects factor, and 'Stimulus intensity', 'Attention' and 'Laterality' as within subject factors.

To evaluate specific effects of variables, significant interaction effects in the full 2 x 2 x 2 x 2 design were followed up with GLM analyses restricted to the interaction terms as well as t-tests, where appropriate. Since we could not compare ipsi- and contralateral stimulation in the four patients with bilateral pain, we excluded these patients and their matched control subjects from the GLM analyses. The GLM analyses were therefore restricted to 2 x 12 subjects. All subjects (2 x 16) were included in calculation of mean VAS scores for painful and non-painful stimuli and mean scores on the MPQ-DLV and MPI-DV questionnaires.

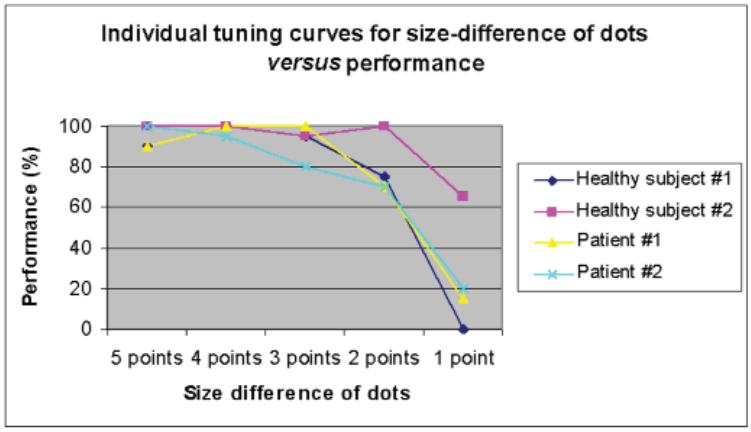

Figure 7.2 Tuning curves for the divided attention task in four individual subjects. This illustrates that a cut-off point of 80% performance represents the minimum difference that a subject can still properly identify, since performance tends to drop sharply with smaller differences.

Performance on the divided attention task was defined by the number of targets that the subject correctly detected, as a proportion of presented targets (hit rate). Again, data were analyzed with GLM for repeated measures, with 'Group' as between-subjects factor and 'Stimulus intensity' and 'Laterality' as within-subject factors.

All data were entered and analyzed in SPSS for Windows (version 15.0). Effects with $p<0.05$ were considered significant. P-values between 0.05 and 0.10 were marked as a trend. For all GLM analyses a mixed-model approach was used.

RESULTS

Pain characteristics

In the patient group, VAS scores for current pain did not correlate significantly with pain thresholds or main effects of 'Attention' and 'Laterality'. We observed a trend for a correlation between current pain (VAS) and mean VAS scores in the experiment (Pearson's $r=0.468$, $p=0.07$).

In the patient group, total scores on the pain rating index and Number of words chosen subscales of the MPQ-DLV did not significantly correlate with total VAS scores or mean pain thresholds. The other results for the MPQ-DLV and MPI-DV are summarized in supplemental table S7.3.

Pain thresholds

GLM analysis on pain threshold values (results shown in table 7.1) revealed a main effect for 'Attention' ($p<0.001$) and an interaction between 'Group' and 'Attention' ($p<0.05$). The effect of attention was larger in controls (pain threshold difference for different attentional states 4.2 mA) than in patients (pain threshold difference 2.7 mA). No effects were observed involving 'Laterality'. There was a trend for overall lower thresholds for pain in patients (25.6 mA, SD 7.28 mA) compared to controls (31.4 mA, SD 9.74 mA) (main group effect, $p=0.06$).

VAS scores during actual experiment

Results from the GLM analysis are shown in table 7.2. Figures 7.3 and 7.4 display VAS scores for the different experimental conditions. As expected, there was a significant main effect of Stimulus intensity ($p<0:001$), in that VAS scores for painful stimuli were higher than for non-painful stimuli (20.42 versus 16.57 mm). No other main effects were observed, but there was a trend for a group effect ($p=0.09$).

The interaction between 'Attention' and 'Laterality' was significant ($p<0.05$), as was the interaction between 'Stimulus intensity', 'Attention' and 'Laterality' ($p<0.01$). We also found a significant interaction between 'Stimulus intensity', 'Attention' and 'Group' ($p<0.05$).

Table 7.1 Repeated-measure general linear model, testing for the main effects of the following factors on pain thresholds, and the interactions between factors: the within-group factors Attention (focused or distracted attention), Laterality of stimulus (symptomatic or contralateral body half) and the between-group factor Group (patient versus control).

	F-value	p-value[a]
Main effects		
Attention	50.00	<0.0005[b]
Laterality	3.65	0.07
Group	3.83	0.06
Interactions		
Attention x Group	4.70	0.04[b]
Laterality x Group	5.04	0.68
Attention x Laterality	2.90	0.10
Attention x Laterality x Group	0.04	0.93

[a] Degrees of freedom (1;22) for all main effects and interactions; [b] $p<0.05$

To further explore the effect of 'Stimulus intensity' in relation to the other factors, we performed two focused GLM analyses: (a) for painful stimuli only, and (b) for non-painful stimuli only; both with 'Group' as the between-subject factor and 'Attention' and 'Laterality' as within-subject factors. In the 'non-painful stimuli'-GLM, we found a significant interaction of 'Attention' and 'Laterality' ($F(1;22)=7.73$; $p=0.011$), but no significant interaction of 'Attention' and 'Group' ($F(1;22)=2.17$; $p=0.155$). In the 'painful stimuli'- GLM, we also found an interaction between 'Attention' and 'Laterality' ($F(1;22)=5.83$; $p=0.025$). In contrast to the non-painful stimuli-GLM, however, we also found a significant interaction between 'Attention' and 'Group'

Table 7.2 Repeated-measure general linear model, testing for the main effects of the following factors on VAS ratings, and the interactions between factors: the within-group factors Stimulus Intensity (painful or non-painful), Attention (modulation of attention: focused or distracted attention), Laterality of stimulus (symptomatic or contralateral body half) and the between-group factor Group (patient versus control).

	F-value	p-value[a]	Partial eta squared[c]
Main effects			
Stimulus Intensity	17.203	<0.0005[b]	0.439
Attention	1.265	0.273	
Laterality	0.198	0.661	
Group	3.085	0.093	
Interactions			
Stimulus Intensity x Group	0.759	0.393	
Attention x Group	0.001	0.980	
Laterality x Group	0.227	0.639	
Stimulus Intensity x Laterality	0.152	0.700	
Stimulus Intensity x Laterality x Group	0.129	0.723	
Stimulus Intensity x Attention	1.483	0.236	
Stimulus Intensity x Attention x Group	4.470	0.046[b]	0.169
Attention x Laterality	4.424	0.047[b]	0.167
Attention x Laterality x Group	2.343	0.140	
Stimulus Intensity x Attention x Laterality	8.800	0.007[b]	0.286
Stimulus Intensity x Attention x Laterality x Group	1.678	0.209	

[a] Degrees of freedom (1;22) for all main effects and interactions; [b] $p < 0.05$; [c] Only for significant effects.

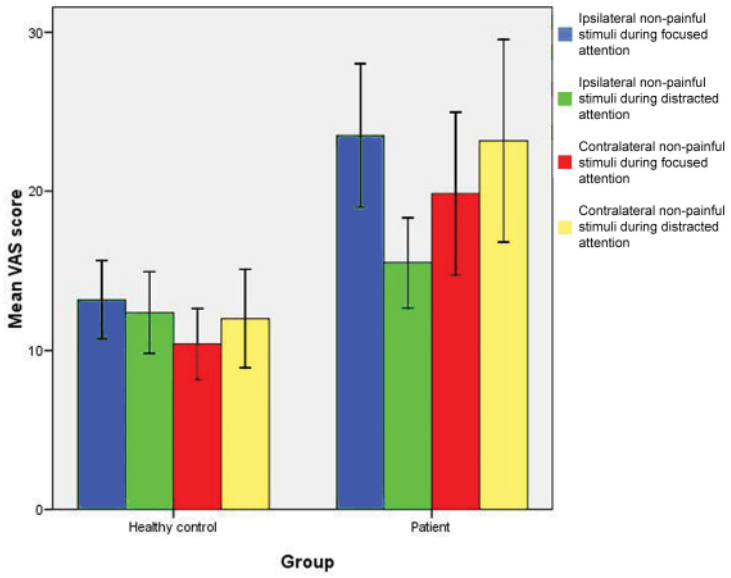

Figure 7.3 Mean VAS scores in pain patients and healthy control subjects for nonpainful stimuli for different attentional states and body sides. Stimulus intensities for non-painful stimuli were based on individually determined pain thresholds. Error bars represent standard error of the mean (SEM).

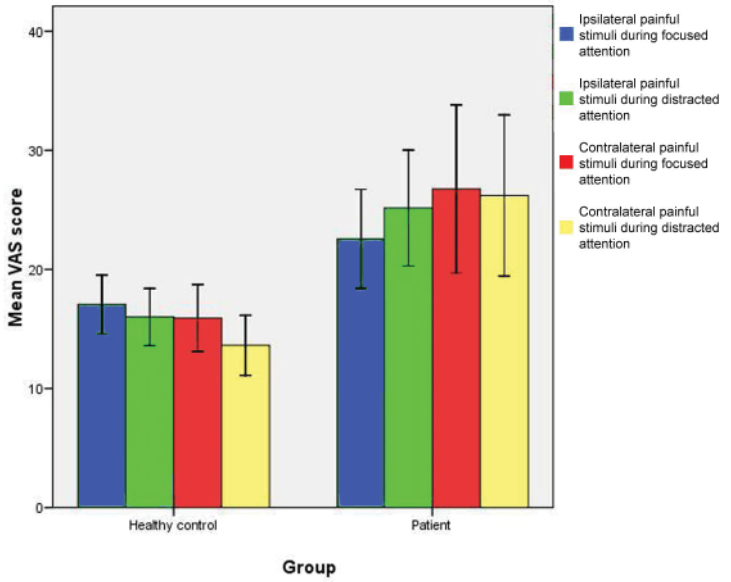

Figure 7.4 Mean VAS scores in pain patients and healthy control subjects for painful stimuli for different attentional states and body sides. Stimulus intensities for painful stimuli were based on individually determined pain thresholds. Error bars represent SEM.

(F(1;22)=4.49; p=0.046). To further investigate this interaction we conducted t-tests, comparing the difference scores for attention (dVAS = VAS during focused attention minus VAS during distraction, collapsed for 'Laterality') between patients and controls, for painful and non-painful stimuli separately. In non-painful stimulation, the effect of 'Attention' did not differ significantly between patients and controls (2.50 ± 6.87 mm versus 0.21 ± 2.10 mm; t=-1.11, p=0.28). By contrast, in painful stimulation we did find a significant between-group difference in the effect of 'Attention' (-1.06 ± 2.55 mm versus 1.16 ± 2.61 mm, t=2.12, p=0.046). This direct comparison in fact reveals an increase of VAS scores (rather than the usual decrease) for patients during painful stimulation (figure 7.5).

Performance

Performance on the divided attention test was good in both groups in all tests (range 74–94%). GLM analysis did not demonstrate any significant main or interaction effects, indicating that performance on the divided attention task was not affected by experimental variables and hence constituted a robust instrument for controlling attention.

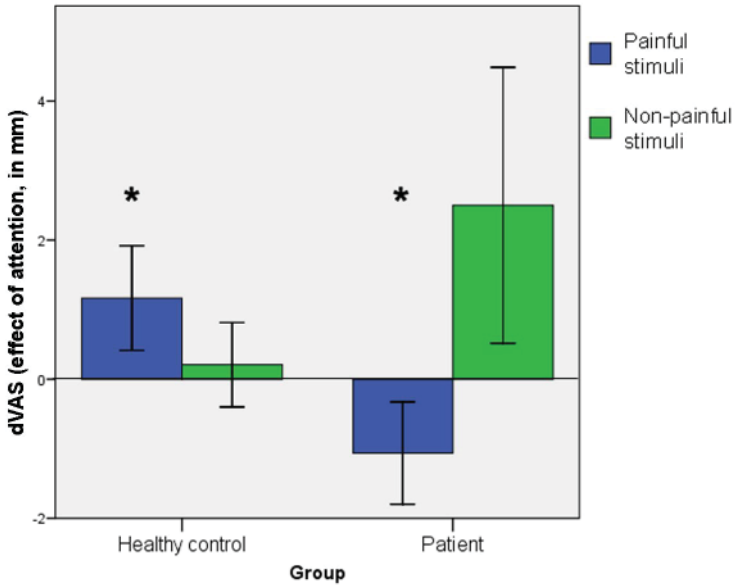

Figure 7.5 The mean effect of attentional manipulation on VAS scores (VAS during focused attention – VAS during distraction) for painful and non-painful stimuli, for both groups. Error bars represent SEM. *p<0.05 for between-group difference in attention-effect.

DISCUSSION

Results and implications

In this experimental psychophysical study, we found that:

1. in patients with chronic, unexplained pain, the effect of attentional manipulation on pain thresholds is smaller than in healthy subjects, with a tendency toward lower pain thresholds in patients;
2. these patients respond abnormally to attentional modulation of pain processing, in that distraction fails to attenuate the perceived intensity of painful stimuli, as it does in control subjects.

These results suggest that pain processing in chronic, unexplained pain is enhanced in a generalized fashion, since we did not observe any significant effects of 'Laterality'. Also, several other findings argue against the idea that abnormal pain processing in patients is restricted to the symptomatic body region: (I) the finding of diminished attention-dependence of pain thresholds (irrespective of laterality) and (II) the site-independent interaction of 'Attention' and 'Group' for rating of painful stimuli. Such generalized enhancement of pain processing has indeed previously been found in fibromyalgia patients, both on a behavioral level and with functional brain imaging.[36,37] Although sensitization is implied in all chronic pain syndromes, the subjective experience of experimental pain in explained forms of chronic pain (e.g. rheumatoid arthritis) is less enhanced than in chronic, unexplained pain.[12]

This study is the first to demonstrate a relative insensitivity to attentional modulation of pain experience in chronic, unexplained pain. This insensitivity can be observed in pain thresholds (smaller effect of attention in patients), as well as in VAS ratings for individualized painful stimuli (a reversed attention-effect). Our finding seems to be largely compatible with the notion of generalized hypervigilance, which supposes an attentional bias in favor of somatosensory stimuli, especially pain.[12,37] This hypervigilance may lead to competition in the allocation of attention between pain and external distracting cues, thus decreasing the influence of such cues. However, the findings of Peters et al. might argue against generalized hypervigilance: they did not find such a disturbed role of attention in the detection of non-painful stimuli in fibromyalgia patients.[17] We also did not detect any disturbance in attention-related processing of non-painful stimuli in patients (although our study was not specifically designed to study non-painful stimulus processing). However, we did demonstrate an overall trend toward higher VAS scores for all stimulus types in patients (painful as well as non-painful), as well as a disturbance in attention-related processing of painful stimuli. This latter finding argues against explanations that do not include attention. Combination of our findings with Peters et al. suggests that generalized hypervigilance in unexplained pain syndromes may be applicable to pain as well as

other sensations,[12] but will be greater with painful than with innocuous stimuli; this is possibly due to their higher threat level, a factor which is known to increase hypervigilance.[38]

Attention does not only influence pain processing, but pain influences the performance on attentional tasks as well, since it automatically calls for attention. This means that distraction tasks can be expected to cause divided attention between pain and another stimulus, rather than total distraction from pain.[34] The attentional bias towards pain is enhanced in chronic pain patients, possibly due to differences in allocation of attentional resources in chronic pain.[39] We could not attribute the decreased influence of distraction in patients to insufficient effort for the attentional task, since patients and controls performed similarly in the divided attention task; this finding argues against the generalized hypervigilance theory, since attention is properly allocated towards the distraction task. An alternative explanation is that distraction does not properly trigger the descending pain modulatory system, which induces pain reduction in healthy subjects.[40] In yet another view, one might argue that our finding on thresholds and VAS scores might point to enhancement (sensitization) at a lower (spinal or peripheral) level. However, this explanation does not account for the attenuated effect of distraction on pain perception, or the abnormalities in pain processing from asymptomatic body regions.

Finally, it might be argued that the reduced effects of attentional modulation in patients are explained by the higher level of pain experience (trend towards higher VAS scores) in patients in response to stimuli. However, this interaction of distraction and pain levels is mostly described at higher absolute levels of pain experience,[10] whereas the absolute pain levels that patients experienced in this study were mild (mean VAS < 30 mm). Furthermore, the level of spontaneous pain symptoms did not correlate with our main outcome measures, although a trend for a correlation between spontaneous pain level and mean VAS scores in the experiment was observed. The latter finding may represent a higher degree of sensitization in more severe pain, although this finding is strictly speaking non-significant and it should be considered exploratory.

The finding of an interaction between 'Attention' and 'Laterality', which was independent of group, seems counterintuitive, since different body sites should not differ in attention-related pain processing in healthy subjects. This may be explained by the fact that ipsilateral body sites were always tested first in the experiment, followed by contralateral sites, giving rise to an order effect. As there were no interactions involving both 'Group' and 'Laterality', it can be assumed that the 'Laterality' order confound was equal for both groups.

Limitations

The investigated population was heterogeneous in age, symptoms and psychosocial status. It might be objected that by 'lumping' patients in this way, we ignore differences between subgroups of patients. The sample size, though sufficient for the study's objectives, is too

small to permit subgroup analyses. However, since we aimed to clarify the role of attention in the pathophysiology of chronic, unexplained pain, without prior assumptions about pathophysiology, we neither included nor excluded patients with a specific syndrome diagnosis, such as fibromyalgia. Yet, our findings are in line with previous studies on hypervigilance in fibromyalgia.[41,42] The female overrepresentation in our sample matches the gender ratio reported in epidemiological studies in chronic pain syndromes.

Excluding patients who used benzodiazepines (because of the well-documented influence of benzodiazepines on attentional processes),[21] might have led to selection bias, since benzodiazepine (over-) use is common in chronic pain and somatoform pain disorder.[43] The inclusion of patients on analgesics, including low-dose opioids was considered unavoidable. Therefore, an influence of analgesics on our findings cannot be excluded. However, we found no significant differences between patients with or without opioid therapy in mean pain thresholds, VAS ratings, or attention-effects on ratings (results not shown).

Our study did not control for phase of the menstrual cycle or other hormonal factors, factors of considerable importance in pain perception.[44] However, the individual-subject matching procedure warrants that the patient and control group are comparable for main age- and sex-related hormonal effects.

The small differences in VAS scores between painful and nonpainful stimuli reflect the small differences in Stimulus intensity (at a minimum, 2 mA at a total Stimulus intensity of 25-31 mA). It follows from this design that pain ratings for non-painful stimuli approximated the ratings for painful stimuli, and thus were significantly higher than zero. However, to obtain a clearer contrast between painful and non-painful stimulation, a future study might use larger differences in Stimulus intensity.

Further study

Whether abnormal attention processing is a primary cause of chronic, unexplained pain, or secondary to another causal factor cannot be deduced from these data. Functional neuroimaging studies are a valuable tool in studying attention-related pain processing (e.g. Ref.[45]), and may contribute to identifying the role of attention (and other cognitive factors) in the etiologic hierarchy of chronic, unexplained pain symptoms,[6,7,46] and the role of abnormal attention- related processing in the descending pain modulatory system.[40] Lastly, imaging studies can provide an objective measure of the functional anatomy in patients with chronic, unexplained pain.

Further studies might identify clinically different subgroups and differences in their pain processing. It is therefore unclear whether our findings can apply to all patients with chronic, unexplained pain. It is also of interest to compare our findings to patients with chronic pain of a known origin, since some studies suggest that pain sensitivity is enhanced in explained

as well as unexplained chronic pain;[12] this may reflect negative affectivity or other common factors. It cannot, on the basis of our data, be excluded that our findings are (in part) a non-specific effect of chronic pain.

In conclusion, patients with chronic, unexplained pain show enhanced pain processing, as well as an attenuated influence of distraction on pain thresholds and on the experience of painful stimuli. These abnormalities are not limited to the symptomatic body region. This supports the notion of a central attention-dependent sensitization process in cerebral pain processing regions, with generalized hypervigilance or abnormal descending pain modulation as possible explanations.

ACKNOWLEDGEMENTS

We thank S. de Jong, M.D., and R. Kunze, M.D., for their help in subject screening and data acquisition; R. Peyron, M.D., for use of data from his research for our study design; Prof. A. Algra, M.D., epidemiologist, and Dr. A.J.M. van Wijck, anesthesiologist/epidemiologist, for their comments on an earlier version of this manuscript.

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. 4th ed. Washington, DC: American Psychiatric Association; 2004.
2. Kerssens JJ, Verhaak PF, Bartelds AI, Sorbi MJ, Bensing JM. Unexplained severe chronic pain in general practice. Eur J Pain 2002;6:203-12.
3. Snijders TJ, de Leeuw FE, Klumpers UMH, Kappelle LJ, van Gijn J. Prevalence and predictors of unexplained neurological symptoms in an academic neurology outpatient clinic - An observational study. J Neurol 2004;251:66-71.
4. Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? Lancet 1999;354:936-9.
5. Peters ML, Vlaeyen JW, Weber WE. The joint contribution of physical pathology, pain-related fear and catastrophizing to chronic back pain disability. Pain 2005;113:45-50.
6. Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, et al. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain 2004;127:835-43.
7. Stoeter P, Bauermann T, Nickel R, Corluka L, Gawehn J, Vucurevic G, et al. Cerebral activation in patients with somatoform pain disorder exposed to pain and stress: An fMRI study. Neuroimage 2007;36:418-30.
8. Veldhuijzen DS, Kenemans JL, de Bruin CM, Olivier B, Volkerts ER. Pain and attention: attentional disruption or distraction? J Pain 2006;7:11-20.
9. McCaul KD, Monson N, Maki RH. Does distraction reduce pain-produced distress among college students? Health Psychol 1992;11:210-7.

10. McCaul KD, Haugtvedt C. Attention, distraction, and cold-pressor pain. J Pers Soc Psychol 1982;43:154-62.

11. Nouwen A, Cloutier C, Kappas A, Warbrick T, Sheffield D. Effects of focusing and distraction on cold pressor-induced pain in chronic back pain patients and control subjects. J Pain 2006;7:62-71.

12. McDermid AJ, Rollman GB, McCain GA. Generalized hypervigilance in fibromyalgia: evidence of perceptual amplification. Pain 1996;66:133-44.

13. Pennebaker JW. The psychology of physical symptoms. New York: Springer-Verlag Inc.; 1982.

14. Lautenbacher S, Rollman GB, McCain GA. Multi-method assessment of experimental and clinical pain in patients with fibromyalgia. Clin Rheumatol 1991;10:168-74.

15. Roelofs J, Peters ML, Zeegers MP, Vlaeyen JW. The modified Stroop paradigm as a measure of selective attention towards pain-related stimuli among chronic pain patients: a meta-analysis. Eur J Pain 2002;6:273-81.

16. Crombez G, Van Damme S, Eccleston C. Hypervigilance to pain: an experimental and clinical analysis. Pain 2005;116:4-7.

17. Peters ML, Vlaeyen JW, van Drunen C. Do fibromyalgia patients display hypervigilance for innocuous somatosensory stimuli? Application of a body scanning reaction time paradigm. Pain 2000;86:283-92.

18. Campbell LC, Clauw DJ, Keefe FJ. Persistent pain and depression: A biopsychosocial perspective. Biological Psychiatry 2003;54:399-409.

19. Fishbain DA, Cutler R, Rosomoff HL, Rosomoff RS. Chronic pain-associated depression: antecedent or consequence of chronic pain? A review. Clin J Pain 1997;13:116-37.

20. Roelofs J, Peters ML, van der Zijden M, Vlaeyen JW. Does fear of pain moderate the effects of sensory focusing and distraction on cold pressor pain in pain-free individuals? J Pain 2004;5:250-6.

21. Koelega HS. Benzodiazepines and vigilance performance: a review. Psychopharmacology 1989;98:145-56.

22. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1:277-99.

23. Verkes RJ, Vanderiet K, Vertommen H, Van der Kloot WA, Van der Meij J. De MPQ-DLV: een standaard nederlandstalige versie van de McGill Pain Questionnaire voor België en Nederland. In: Kloot WA van der, Vertommen H, editors. De MPQ-DLV. Een standaard nederlandstalige versie van de McGill Pain Questionnaire. Achtergronden en inleiding.Lisse: Swets & Zeitlinger BV; 1989. p. 57-74.

24. Kerns RD, Turk DC, Rudy TE. The West Haven-Yale Multidimensional Pain Inventory (WHYMPI). Pain 1985;23:345-56.

25. Lousberg R, Van Breukelen G.J., Groenman NH, Schmidt AJ, Arntz A, Winter FA. Psychometric properties of the Multidimensional Pain Inventory, Dutch language version (MPI-DLV). Behav Res Ther 1999;37:167-82.

26. Sheehan D, Janavs J, Baker R, Harnett-Sheehan K, Knapp E, Sheehan M. M.I.N.I. PLUS. M.I.N.I. internationaal neuropsychiatrisch interview. Nederlandse versie 5.0.0. [vertaling in het Nederlands door: Vliet IM van, Lerou J, Megen HJGM van]. Utrecht: UMC Utrecht; 2000.

27. Dowman R. Effects of interstimulus interval on scalp topographies evoked by noxious sural nerve stimulation. Psychophysiology 1996;33:398-408.

28. Porro CA, Baraldi P, Pagnoni G, Serafini M, Facchin P, Maieron M, et al. Does anticipation of pain affect cortical nociceptive systems? J Neurosci 2002;22:3206-14.

29. Hsieh J-C, Stone-Elander S, Ingvar M. Anticipatory coping of pain expressed in the human anterior cingulate cortex: a positron emission tomography study. Neurosci Lett 1999;262:61-4.

30. Ploghaus A, Tracey I, Gati JS, Clare S, Menon RS, Matthews PM, et al. Dissociating pain from its anticipation in the human brain. Science 1999;284:1979-81.

31. Sawamoto N, Honda M, Okada T, Hanakawa T, Kanda M, Fukuyama H, et al. Expectation of pain enhances responses to nonpainful somatosensory stimulation in the anterior cingulate cortex and parietal operculum/posterior insula: an event-related functional magnetic resonance imaging study. J Neurosci 2000;20:7438-45.

32. Fruhstorfer H, Lindblom U, Schmidt WG. Method for quantitative estimation of thermal thresholds in patients. J Neurol Neurosurg Psychiatry 1976;39:1071-5.

33. Ramsey NF, Jansma JM, Jager G, Van Raalten T, Kahn RS. Neurophysiological factors in human information processing capacity. Brain 2004;127:517-25.

34. Seminowicz DA, Davis KD. A re-examination of pain-cognition interactions: implications for neuroimaging. Pain 2007;130:8-13.

35. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of Visual Analogue Scales as ratio scale measures for chronic and experimental pain. Pain 1983;17:45-56.

36. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002;46:1333-43.

37. Rollman GB, Lautenbacher S. Hypervigilance effects in fibromyalgia: pain experience and pain perception. In: Værøy H, Merskey H, editors. Progress in fibromyalgia and myofascial pain. 1st ed. Amsterdam: Elsevier; 1993. p. 283-309.

38. Koster EH, Crombez G, Van Damme S, Verschuere B, De Houwer J. Does imminent threat capture and hold attention? Emotion 2004;4:312-7.

39. Veldhuijzen DS, Kenemans JL, van Wijck AJ, Olivier B, Kalkman CJ, Volkerts ER. Processing capacity in chronic pain patients: a visual event-related potentials study. Pain 2006;121:60-8.

40. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron 2007;55:377-91.

41. Carrillo-de-la-Pena MT, Vallet M, Perez MI, Gomez-Perretta C. Intensity dependence of auditory-evoked cortical potentials in fibromyalgia patients: a test of the generalized hypervigilance hypothesis. J Pain 2006;7:480-7.

42. Crombez G, Eccleston C, Van den Broeck A, Goubert L, Van Houdenhove B. Hypervigilance to pain in fibromyalgia: the mediating role of pain intensity and catastrophic thinking about pain. Clin J Pain 2004;20:98-102.

43. American Psychiatric Association. Somatoform disorders. In: American Psychiatric Association, editor. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. 4th ed. Washington, DC: Americal Psychiatric Association; 2004. p. 445-71.

44. Hapidou EG, Rollman GB. Menstrual cycle modulation of tender points. Pain 1998;77:151-61.

45. Peyron R, Garcia-Larrea L, Gregoire MC, Costes N, Convers P, Lavenne F, et al. Haemodynamic brain responses to acute pain in humans: sensory and attentional networks. Brain 1999;122 (Pt 9):1765-80.

46. Kwan CL, Diamant NE, Pope G, Mikula K, Mikulis DJ, Davis KD. Abnormal forebrain activity in functional bowel disorder patients with chronic pain. Neurology 2005;65:1268-77.

SUPPLEMENTARY TABLES

Supplementary table S7.1 Inclusion and exclusion criteria for patients

Inclusion criteria	Exclusion criteria
(a) pain symptoms of one or more limbs;	(a) age under 18;
(b) pain as the main reason for visiting the clinic;	(b) insufficient command of the Dutch language;
(c) duration of symptoms for six months or more;	(c) a psychiatric Axis-1-disorder (except pain disorder, which is almost ubiquitous in this population), as evaluated by using the MINI International Neuropsychiatric Interview (MINI Plus);[26]
(d) disability in professional, social or other relevant fields of functioning due to pain;	(d) use of benzodiazepines, because of a possible effect on performing sustained attention tasks.[21]
(e) absence of an identifiable disease or somatic cause of the symptoms.[a]	

[a] See text for details of diagnostic procedure.

Supplementary table S7.2 Patient characteristics

	Age (y)	Gender	Pain location (L = left, R = right)	Pain diagnosis[a]	Pain duration (years)	Current VAS score (mm)[b]	On social support for pain-related disability?	Analgetic medication use
1	54	F	Shoulders + upper arms	-[d]	20.0	19	Yes	Ibuprofen
2	68	F	Lower legs + feet [c]	-	2.0	21	No (retired)	Paracetamol
3	32	M	Low back + L upper leg	Pseudoradicular syndrome [d]	3.0	31	No	none
4	38	F	Back + upper legs + L calve	Post-laminectomy syndrome [d]	22.0	77	Yes	acetylsalicylic acid, tramadol
5	47	F	Back + upper legs + R lower leg	Pseudoradicular syndrome [d]	25.0	18	Yes (partial compensation)	ibuprofen
6	35	F	Back + dorsal side of legs [c]	Pseudoradicular syndrome	0.8	74	Yes (temporary sick leave)	codeine
7	42	M	Neck + back + L shoulder + L arm	Chronic widespread pain [d]	1.5	59	Yes	paracetamol
8	64	F	Arms + hands + R lower leg	Diffuse joint pain	7.0	21	Yes	Amitriptylin
9	55	M	Back + R leg + L shoulder	Pseudoradicular syndrome	5.0	38	No	paracetamol
10	55	F	Back + L leg	Post-laminectomy syndrome	45.0	32	No (housekeeper)	rofexocib, gabapentin, paracetamol
11	63	M	L lower leg + L heel	Somatoform pain disorder [d]	1.5	96	Yes	none
12	46	F	R chest + L leg	Somatoform pain disorder [d]	1.5	88	Yes (partial compensation)	rofecoxib, oxycodon, paracetamol
13	23	F	Generalised pain, most in lower arms [c]	Fibromyalgia [d]	2.5	74	Yes (temporary sick leave)	Tramadol
14	49	F	Lower back + L flank + legs [c]	Somatoform pain disorder [d]	1.9	63	Yes	paroxetin
15	61	M	L arm, R groin	Chronic widespread pain	0.8	44	No (retired)	none
16	28	F	Neck + R arm	-	0.9	28	No	ibuprofen

[a] In cases where a (syndrome) diagnosis of pain symptoms was stated, it is mentioned here for purposes of information. However, syndrome diagnosis was not considered as a inclusion or exclusion criterion.
[b] Visual analogue scale.
[c] Symmetrical distribution of limb pain.
[d] In these patients, either the patient or their physician considered psychological factors to be of considerable importance of onset, severity, exacerbation or maintenance of pain symptoms, thereby fulfilling criteria for the DSM-diagnosis of somatoform pain disorder.(American Psychiatric Association 2004a) In certain cases, this was the only clinical diagnosis.

Supplementary table S7.3 Results from the McGill Pain Questionnaire (Dutch Language version) and the Multidimensional Pain Inventory (Dutch Version) in the patient group

Scale/subscale (extremes)	Median score	Range of scores
MPI-DV *(all scores range from 0-6)*		
Pain intensity	3.5	2 – 5
Interference	3.4	1 – 6
Life control	4.8	2 – 6
Affective distress	1.0	0 – 4
Support	4.5	2 – 6
Punishing responses	0.0	0 – 5
Solicitous responses	3.3	1 – 6
Distracting responses	2.5	1 – 5
Household chores	3.9	2 – 6
Outdoor work	0.6	0 – 6
Activities away from home/Social activities	2.6	2 – 6
General activity	2.5	2 – 4
MPQ-DLV *(extremes in brackets)*		
Current VAS score (0 – 100)	41.0	18 – 96
Minimum VAS score (0 – 100)	17.0	2 – 83
Maximum VAS score (0 – 100)	87.0	49 – 100
Pain rating index – sensory	9.5	3 – 23
Pain rating index – affective	2.0	0 – 5
Pain rating index – evaluative	5.5	0 – 8
Pain rating index – total score	16.5	6 – 35
Number of words chosen – sensory	6.5	2 – 12
Number of words chosen – affective	1.5	0 – 3
Number of words chosen – evaluative	3.0	0 – 3
Number of words chosen – total score	10.0	3 – 18
Quality of life index	12.0	4 – 103

8

Abnormal prefrontal pain modulation in chronic, unexplained pain

Tom J. Snijders
Matthijs Vink
Frank Koerselman
Jan van Gijn
Nick F. Ramsey

Submitted for publication

ABSTRACT

Background: Chronic, unexplained pain is a common but ill-understood clinical problem, with a complex biopsychosocial background. Abnormal pain processing in the central nervous system and increased attention towards pain are often implied in the pathophysiology of chronic, unexplained pain. To test the hypothesis that the pain experience in chronic, unexplained pain is linked to impaired top-down inhibitory regulation, we investigated the cerebral processing of painful stimuli during distraction from pain.

Methods: We performed an event-related functional MRI-study in 12 patients with chronic, unexplained, unilateral limb pain, and in 12 matched healthy controls. Subjects underwent painful and non-painful stimulation (subjective intensity matched) in the painful body region as well as in the contralateral, asymptomatic region, while performing a cognitively demanding distraction task.

Results: In healthy controls, the effects of pain during distraction were associated with activity in certain brain regions of the pain matrix, including the right dorsolateral prefrontal cortex and other prefrontal areas. In patients, the prefrontal response to painful stimuli was significantly reduced, whereas activation of sensory-discriminative areas (including operculo-insular cortex) was enhanced. These abnormalities were most prominent during stimulation of the painful body region, but were also found contralaterally. Posthoc analysis revealed a significant increase of connectivity during pain between prefrontal regions and operculo-insular cortex in patients.

Conclusions: Painful stimulation during distraction in patients with chronic, unexplained pain is associated with abnormal cerebral pain processing, implying dysfunction of the prefrontal pain modulation system that usually causes suppression of pain perception during distraction.

INTRODUCTION

Chronic pain is a major general health problem, affecting 15-20% of the general population. In a substantial proportion of these patients, no adequate medical explanation can be identified on medical evaluation.[1] In clinical practice, different descriptive terms are in use, such as fibromyalgia and irritable bowel syndrome. However, criteria for these syndromes are often arbitrary, and the many similarities support the view that they form a spectrum of chronic, unexplained (or: 'functional') pain syndromes.[2,3] Chronic, unexplained pain (CUP) patients report a poor quality of life and account for extensive health care consumption.[4] Given the limited knowledge on causal and contributing factors, rational treatment options are limited and results of treatment are often unsatisfactory. A better understanding of the pathophysiology is urgently needed for the development of more effective treatment strategies.

Many neurobiological and psychological factors have been postulated in chronic pain syndromes. A dominant view is that abnormal attentional bias towards somatosensory stimuli may underlie CUP. The theory of 'generalised hypervigilance' implies that this attentional bias leads to a more intense perception of aversive sensory stimuli.[5,6] This is supported by reports from psychophysical studies of increased sensitivity to painful and other stimuli in CUP, as well as of absence of pain attenuation that normally results from distraction.[7,8] Enhancement of the pain signal also seems to be spatially generalised, i.e. not limited to the painful body region.[7]

Functional neuroimaging provides a means to investigate neurophysiological processing of pain in healthy subjects and in clinical pain conditions,[9,10] as well as the influence of specific factors such as attention or mood on pain processing. In this study, we used functional MRI (fMRI) to compare cerebral pain processing between CUP patients and matched healthy volunteers.

We recently showed that patients with CUP differed most from controls in their inability to attenuate pain during distraction from pain.[7] In order to further study this between-group difference in pain experience during distraction at the cerebral level, we chose to distract subjects continuously from sensory stimuli by an audiovisual distraction task. This careful manipulation of the subjects' attentional state, together with matching of subjective pain levels between patients and controls, as well as a dedicated experimental design (rapid event-related fMRI) all contribute to isolation of cerebral pain processing from possible confounders in this experiment. We studied the extent of presumed abnormalities in cerebral pain processing by comparing processing of painful stimuli applied in painful body regions with those in asymptomatic body regions. We hypothesized that increased pain sensitivity towards pain during distraction in CUP is mediated by a generalised (body region-independent) pattern of dysfunctional cerebral pain modulation, corresponding to abnormal prefrontal brain activity.

MATERIALS AND METHODS

Subjects

Twelve CUP patients, recruited prospectively from Neurology and Pain Medicine outpatient clinics, participated in the study. They suffered for ≥6 months from pain, for which routine medical evaluation, including medical history and appropriate ancillary investigations, failed to show a conventional medical cause. A diagnosis of a functional pain syndrome such as fibromyalgia was neither mandatory for inclusion nor a ground for exclusion. All patients reported continuous pain (no pain-free intervals), including on testing days. In order to compare clinically painful body regions with corresponding painless body regions, we selected patients who suffered from pain in any limb (this body region is further labelled 'IPSI-SYMPTOMATIC') and who experienced no pain in the contralateral limb (further labelled 'CONTRA-ASYMPTOMATIC'); a more widespread distribution of pain than just the IPSI-SYMPTOMATIC limb was allowed as long as the CONTRA-ASYMPTOMATIC limb was pain-free. Patients using benzodiazepines or high-dose opioids (>30 mg morphine or equivalent) were excluded because of possible interference in execution of the attention task.[11]

Twelve pain-free volunteers without a history of psychiatric or neurological disease served as healthy control subjects. They were matched for age (<3 year age difference) and sex. All subjects were right-handed.

The local medical ethics committee of the University Medical Center Utrecht, The Netherlands, approved the study, in accordance with the Declaration of Helsinki (2008). All subjects provided written informed consent.

Stimuli

The symptomatic (IPSI-SYMPTOMATIC) and corresponding contralateral (CONTRA-ASYMPTOMATIC) body regions for stimulus application were selected from the patients' own drawings of pain regions; controls underwent stimulation in the same region as their matched patient. Stimuli were applied with a transcutaneous electrical nerve stimulator (Elpha2000®, Danmeter). Stimuli consisted of short pulse-trains (frequency 10 Hz, pulse-width 250 μs, pulse-train-duration 700 ms). During MRI-scanning, shielded electrodes and cables and a low-pass filter (Tesch® A14x23) were used to minimize electrically induced MRI-artefacts. Within the region of pain symptoms from the patients' own drawings, we applied test stimuli at different locations until we found a suitable stimulus location in which (a) subjects described the sensation at higher stimulus intensities (see below) to be 'burning or pricking' in nature; (b) the subject did not report radiation of the sensation towards distant body regions; (c) no relevant motor response was observed.

Pain thresholds and scores

We determined individual pain thresholds by applying series of stimuli with ascending and descending intensity, each rated by the subject as painful or non-painful.[12] Stimulus intensities were then defined as *Painful* (pain threshold+5 mA) or *Non-painful* (pain threshold-5 mA), separately for IPSI-SYMPTOMATIC and CONTRA-ASYMPTOMATIC regions (total of 4 stimulus types).

In the MRI scanner, patients again rated the painful and non-painful stimuli before actual scanning on a visual analogue scale (VAS, range 0 ('no pain at all') to 100 mm ('worst pain imaginable')). When differences in VAS-scores between painful and non-painful stimuli were less than 5 mm (in 3 patients and 4 controls), painful stimulus intensity was increased with 5 mA-steps until the VAS-difference was ≥5 mm. We did not record VAS scores during scanning, either for the stimulus-induced pain or for the patients' clinical pain symptoms, to avoid attentional bias towards pain instead of the intended attentional focus towards the distraction task.

Distraction task

All subjects were continuously distracted from electrical stimuli by means of a *divided attention* task. In this cognitively demanding combined audiovisual oddball paradigm,[13] subjects are asked to attend simultaneously to dots on a screen and to beeps from a headphone, and to press a button in case of an oddball (smaller/larger dot or higher/lower beep). Subjects underwent a threshold test beforehand to determine the optimum difference in size or pitch between standard signals and oddballs, i.e. the difference that led to task performance of 70-80%, in order to achieve optimum attentional engagement in the task.[13] Therefore, performance/accuracy reflects the degree of attention allocated to the task.

Scanning session

During MRI scanning, subjects received 7 stimulus blocks of ~2 min duration, in which the electrical stimuli and the distraction task were simultaneously presented. These blocks were interchanged with rest blocks (30 sec) without any electrical stimuli or distraction task. During the stimulus blocks, the four types of electrical stimuli (painful and non-painful, for IPSI-SYMPTOMATIC and CONTRA-ASYMPTOMATIC side, respectively) were presented in pseudorandom order and with a jittered inter-stimulus-interval of either 3.0, 4.5 or 6.0 s, to minimize the subjects' anticipation of stimuli, and to optimize efficiency of this rapid event-related design.[14] We applied an average of 24 stimuli (4 stimulus types x 6 stimuli) in each of the seven stimulus blocks, corresponding to a total of 168 stimuli. Performance on the divided attention task was recorded for the test session before scanning, and for each of the scanning blocks.

MRI acquisition

All images were acquired on a 3 Tesla clinical MRI-scanner (Philips Achieva®), with a PRESTO-SENSE fMRI-protocol,[15] which allows rapid scanning of the complete brain through parallel imaging. Each session consisted of two runs, with a total of 1324 functional T2*-weighted scans (duration 750 ms, TR 22.7 ms, TE 33.4 ms, flip angle 10°, FOV 224x256x160 mm, voxel size 4x4x4 mm). A T2*-weighted scan with higher anatomical resolution was obtained for co-registration of functional scans with a T1-weighted anatomical scan (voxel size 1x1x1 mm).

fMRI analysis

Data preprocessing and analysis per subject (first level) were performed with SPM5. We first performed visual inspection for major motion artefacts, which did not occur in any subjects, and manual reorientation of images (if needed) to approximate standard (Montreal Neurological Institute (MNI) space) orientation. Preprocessing then consisted of realignment of all functional images to the high-resolution T2* scan, coregistration of the high-resolution T2* scan (and all functional images) with the anatomical scan, simultaneous segmentation and normalization to match the 2 mm-resolution MNI template brain included in the SPM5 package (unified segmentation procedure), and image smoothing (FWHM 8 mm).

For each subject, we modelled the brain activation associated with non-painful and painful stimuli per body region (resulting in four factors, modelled as events) by convolving the onsets with the hemodynamic response function. We added individual realignment parameters as six nuisance regressors to the model.

A high-pass filter with a cut-off of 161 s for the first run and 171 s for the second run (optimized for design efficiency) was applied. Next, we calculated contrast maps for the *pain-effect* (painful minus non-painful stimuli) for both the IPSI-SYMPTOMATIC and the CONTRA-ASYMPTOMATIC region.

Group analyses of the pain-effects for both body regions were performed with MULTISTAT.[16] This method constitutes a mixed-effect analysis through combining the estimated statistical effects and the standard deviations per subject. We calculated group maps for the pain-effects, separately for patients and control subjects, and a map for the between-group comparison (patients minus controls). Significance level was set at $p<0.05$, corrected for multiple comparisons (corresponding with T-values$\geq$5, cluster threshold 10 voxels).

Seven patients suffered from right-sided pain symptoms, five from left-sided symptoms. Since cerebral pain processing in healthy subjects is partially characterized by activation of brain regions contralateral to the painful stimulus site (in addition to regions that activate bilaterally or mostly right-sided),[17] we repeated group analyses with right-left flipping of contrast maps for pain-effect for all patients and matched controls who underwent left-sided IPSI-SYMPTOMATIC

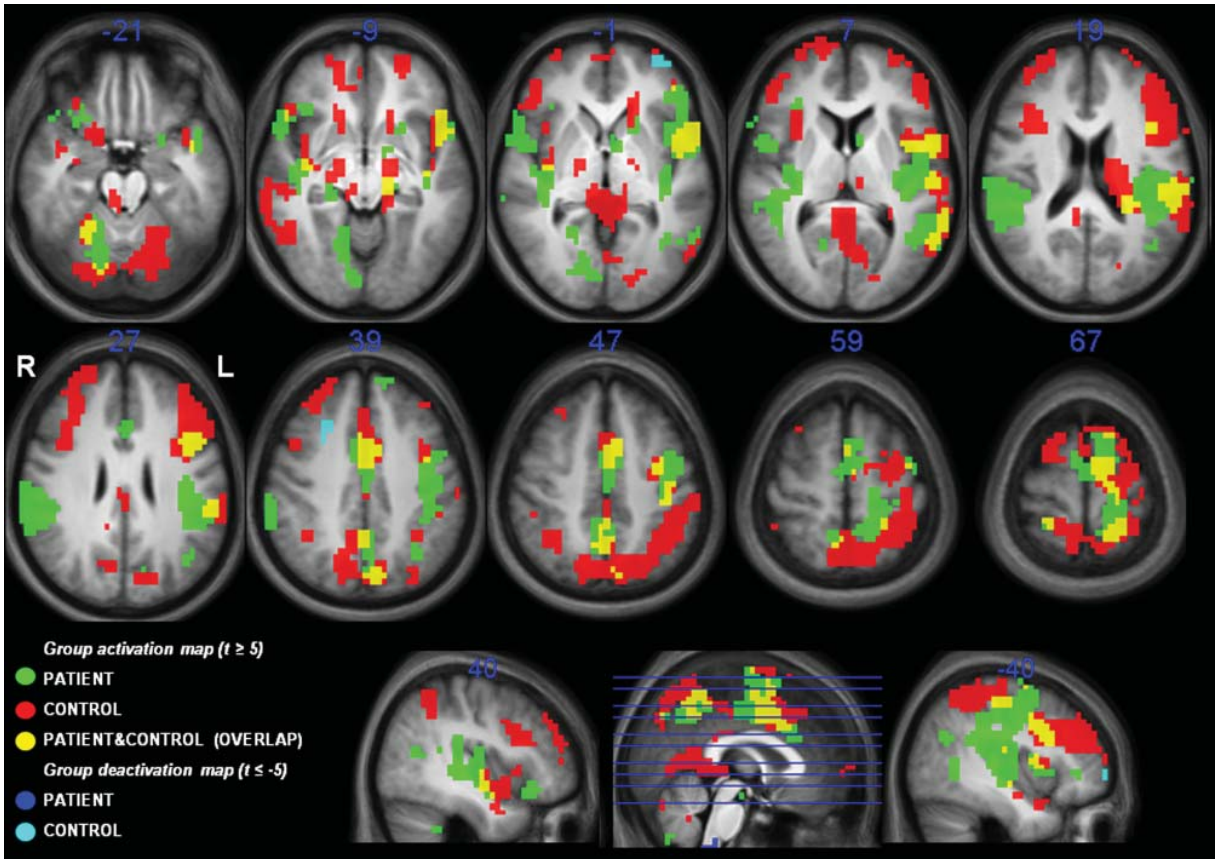

Figure 8.1 fMRI contrast map for the pain-effect (painful *minus* non-painful stimuli) during stimulation of the IPSI-SYMPTOMATIC (=symptomatic) body region in CUP patients and control subjects. All images (transverse slices, slice numbers represent z coordinate in MNI space) in figure 8.1-8.2-8.3-8.4 are presented in radiological orientation, with fMRI maps superimposed on a mean image of normalized (to the MNI template brain) T1-weighted anatomical scans from all subjects.

stimulation. This analysis did not reveal additional activation sites in comparison with regular group analyses (results not presented).

Because of the differences in laterality of symptoms between subjects, we did not directly compare activations for IPSI-SYMPTOMATIC and CONTRA-ASYMPTOMATIC pain; the results of such an analysis would be difficult to interpret given the distribution of cerebral responses to pain (either contralateral to the stimulus, bilateral, or right-sided), which may lead to dilution of regional effects within and between groups.

Connectivity analysis

We performed a psychophysiological interaction (PPI) analysis to look for CUP-specific patterns of functional connectivity between brain regions involved in pain processing. PPI provides an estimate of the changes in functional connectivity between a pre-specified ('seed') region and other brain regions ('sinc' regions, whole-brain analysis) in response to different tasks or stimuli.[18] We selected seed regions that (a) have an established role in pain processing;[9,10] and (b) show a between-group difference in the primary contrast of interest, i.e. the IPSI-SYMPTOMATIC pain-effect contrast. Individual PPI maps were calculated and entered in second-level (group) analysis in SPM5 to investigate group effects and group differences. For this exploratory analysis, significance level was set at $p<0.001$ (uncorrected) with a cluster threshold of 3 voxels.

RESULTS

Group description (table 8.1)

Most patients suffered from a pseudoradicular pain syndrome of an arm or leg, in combination with low back pain or neck pain.

Behavioural measures

Pain thresholds did not differ between groups (patients versus controls: 31.1 mA versus 29.6 mA for ipsilateral stimuli, p=0.60; 31.9 versus 31.1 mA for contralateral stimuli, p=0.57, independent-sample t-test).

Thresholds for detecting oddballs did not differ between groups (auditory: p=0.62; visual: p=0.35). Performance on the divided-attention task was similar for patients and controls, both before fMRI scanning (77 versus 83%, p=0.79; Mann-Whitney test) and during scanning (63 versus 65%, p=0.71). There was a trend for a decrease in performance on the divided attention-task during fMRI scanning (p=0.08), but this decrease was similar for patients and controls. Attentional manipulation was thus equally effective in patients and controls.

Table 8.1 Patient characteristics

Patient no.	Age (y)	Gender	Clinical pain syndrome	Stimulus location (IPSI-SYMPTOMATIC)	Analgesic medication	Pain duration (months)	VAS score for current pain (mm)
1	41	Female	Low back pain + pseudoradicular leg pain	Right hand	Paracetamol/codeine	91	67
2	29	Female	CUP, not otherwise specified	Right arm	None	32	28
3	48	Male	Chronic widespread pain	Left arm	Ibuprofen	324	59
4	38	Male	Low back pain + pseudoradicular leg pain	Left leg	None	114	31
5	28	Female	Chronic widespread pain/Pain disorder	Right leg	None	89	74
6	51	Female	Neck pain + pseudoradicular arm pain	Right arm	None	36	45
7	50	Female	Pseudoradicular leg pain	Right leg	Venlafaxine, Paracetamol, Amitriptylin	18	51
8	58	Female	vulvodynia + pseudoradicular leg pain	Left leg	Amitriptylin, Tramadol/ paracetamol	60	68
9	53	Female	Neck pain + pseudoradicular arm pain	Right arm	Fentanyl, Paracetamol, Naproxen, Pregabaline, Venlafaxine	72	62
10	48	Female	Pseudoradicular leg pain	Left leg	Paracetamol	36	80
11	37	Male	Pseudoradicular leg pain	Left leg	Ibuprofen	22	Missing
12	53	Male	Postoperative CUP	Right arm	Ibuprofen	120	62
Median	48	M:F = 4:8		Left:Right = 5:7		66	62

CUP = chronic, unexplained pain.

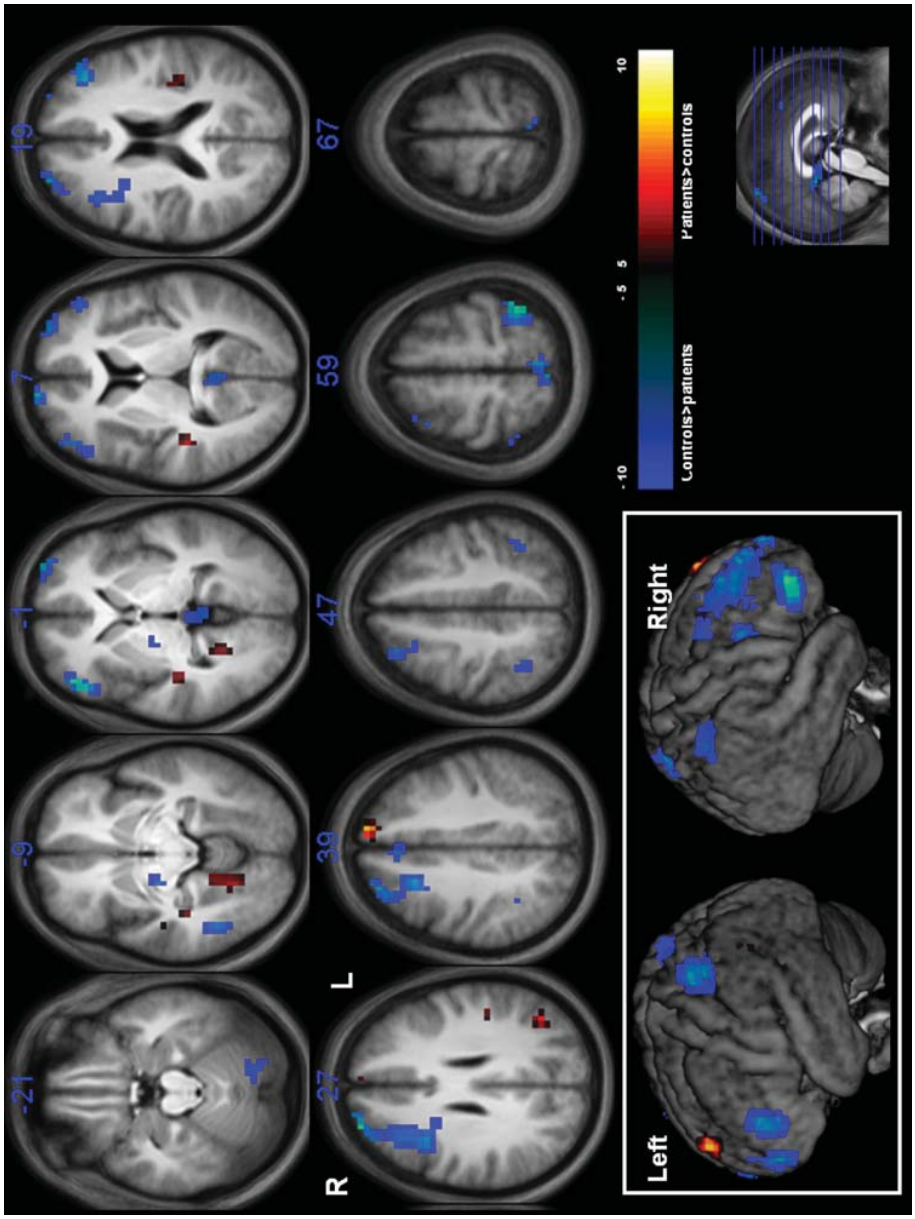

Figure 8.2 Group comparison of the pain-effect (painful *minus* non-painful stimuli) during stimulation of the IPSI-SYMPTOMATIC body region. Warm- and cold-coloured regions represent group differences in activity. Transverse slices, and 3D-rendering of surface of left and right hemisphere (box).

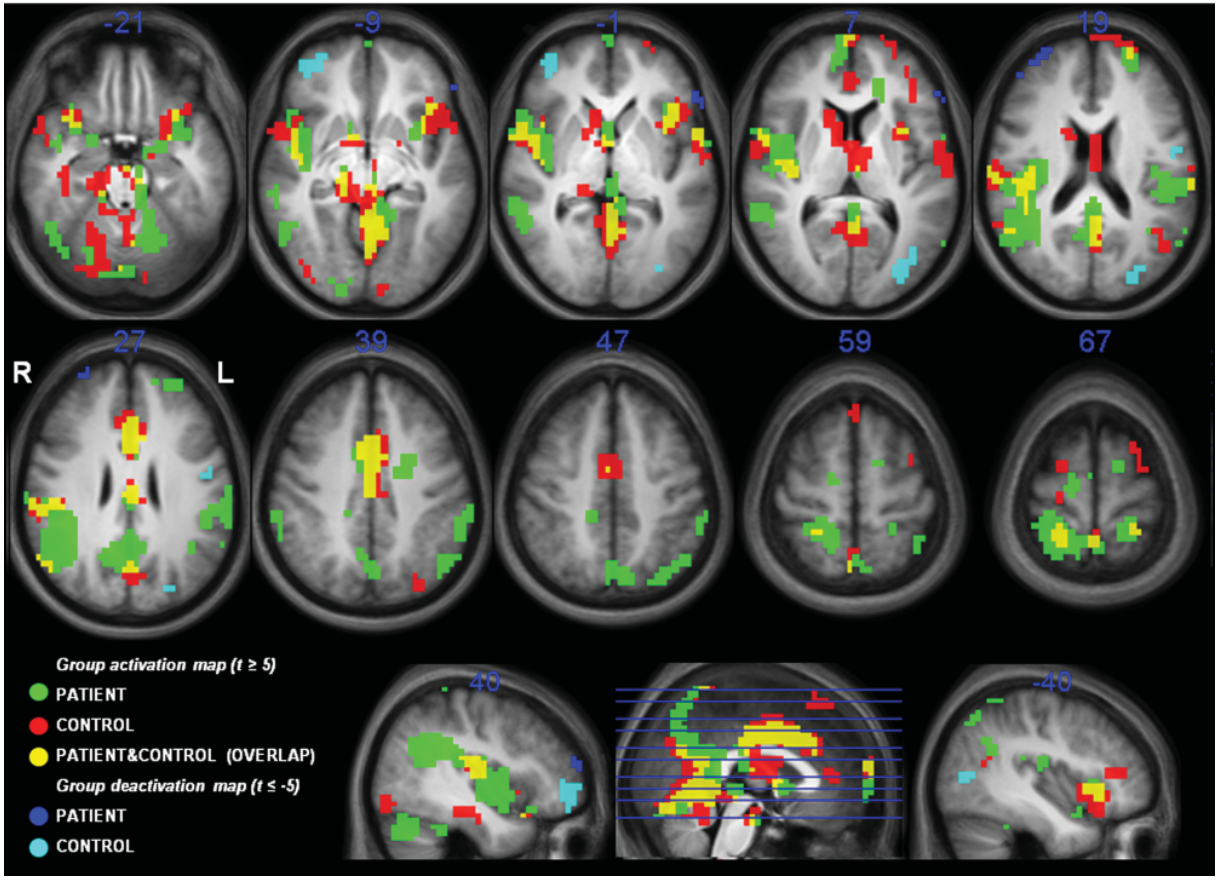

Figure 8.3 fMRI contrast map for the pain-effect (painful *minus* non-painful stimuli) during stimulation of the CONTRA-ASYMPTOMATIC body region in CUP patients and control subjects.

fMRI analysis

IPSI-SYMPTOMATIC body region (figure 8.1, supplementary table 8.1)

In healthy controls, the pain-effect contrast (=painful minus non-painful stimuli) revealed activation of well-known pain processing regions, including bilateral primary (S1) and left secondary somatosensory cortex (S2), left posterior insula (pINS), bilateral dorsolateral prefrontal cortex (DLPFC), and anterior (ACC) and posterior cingulate cortex (PCC). In CUP patients, the pain processing regions most prominently activated were bilateral operculo-insular cortex (S2/pINS), medial prefrontal cortex and ACC.

Direct comparison of the pain-effect at the IPSI-SYMPTOMATIC region between groups showed significantly higher activity levels in patients than in controls in right S2/pINS, left S2, right lingual gyrus, left angular gyrus, and left superior frontal gyrus (figure 8.2, supplementary table 8.1). Conversely, we found significantly lower activity levels in patients than in controls in bilateral DLPFC, several bilateral parietal regions, right thalamus, PCC, bilateral superior frontal gyrus, right inferior temporal gyrus and left cerebellar hemisphere.

CONTRA-ASYMPTOMATIC body region (figure 8.3, supplementary table 8.2)

In controls, pain-effect contrast maps for CONTRA-ASYMPTOMATIC stimulation feature pain processing regions similar to stimulation on the ipsilateral side. In patients, activity patterns again show prominent activity in bilateral S2/pINS.

Upon direct group comparison of the CONTRA-ASYMPTOMATIC pain-effect (figure 8.4, supplementary table 8.2), significantly higher levels of activity in patients occurred in left angular gyrus, right precuneus, left SMA and left rostral ACC. Activation levels were significantly lower in patients in right cuneus, left IFG, left middle occipital gyrus, right DLPFC, and left transverse temporal gyrus.

From the differences between groups that we found in the analysis of pain-effect, it cannot be distinguished whether higher contrast values in one group are the effect of higher activity in that group during painful stimuli, or the effect of lower activity in that group during non-painful stimulation. To visualize the directionality of the major effects we found, we performed a post-hoc ROI analysis with right DLPFC and left S2/pINS as ROI's, since these regions most consistently showed between-group differences in the primary analysis for ipsilateral pain-effect. We calculated mean activity during ipsilateral painful and non-painful stimuli with the MarsBar toolbox for SPM.[19] The group means for these activity levels are depicted in figure 8.5. These results demonstrate that the differences in pain effect between groups are the consequence of different activity levels during painful stimulation and do not result from differences in activity during non-painful stimuli, since activity levels in right DLPFC and left S2/pINS are very similar for both groups during non-painful stimuli.

Connectivity analysis (figure 8.6, supplementary table 8.3)

We selected two seed regions that showed significant differences in activity between groups for PPI analysis: right-sided DLPFC (activations in patients<in controls) and left-sided S2/pINS (activation in patients>in controls).

PPI analysis with right DLPFC as seed region showed that connectivity during pain from this seed region with left orbitofrontal cortex (OFC) is significantly greater in patients than in controls, with positive task-related connectivity between regions in patients but not in controls. With left S2/pINS as a seed region, the task-related connectivity with left ACC is also marginally stronger than in controls, with positive task-related connectivity between regions only in patients.

DISCUSSION

In this functional MRI study of pain processing during distraction, we found differences in brain activation patterns between CUP patients and matched healthy controls. In the patient group, the effects of painful stimulation, applied at the symptomatic body region, were associated with abnormally high levels of brain activation in bilateral operculo-insular cortex, in the right lingual gyrus and in certain prefrontal brain regions. In contrast, brain activity in patients was significantly lower in regions that are commonly associated with emotional-evaluative aspects of pain processing and attention (bilateral DLPFC, mid-parietal, PCC), as well as in other pain processing regions (right thalamus, left cerebellum).[9] Stimulation of the contralateral (non-symptomatic) body region in CUP patients resulted in a similar attenuation of prefrontal brain activity as in the symptomatic region.

In the present study, subjective stimulus intensities were matched for patients and controls. We applied a distraction task throughout the experiment to control for attentional state and to create circumstances that, in a previous study, resulted in the greatest contrast in pain processing between groups.[7] The distraction task resulted in equally effective distraction of patients and controls. Both the attentional manipulation and the stimulus matching add to the specificity of our findings; differences between groups reflect context-specific (distraction-specific) differences in pain processing between CUP patients and controls. This means that even in the context of comparable distraction from pain and similarly perceived pain intensity, brain activity patterns differed between CUP patients and controls, implying that our findings truly reflect cerebral pain processing in CUP.

The similar pain thresholds we found in patients and controls may seem to argue against (cerebral) pain amplification in CUP, but this finding is most likely due to the stimulus location, which was based on a patient's individual pain localisation and was matched in the corresponding control subject. Small individual variations in exact location were made in

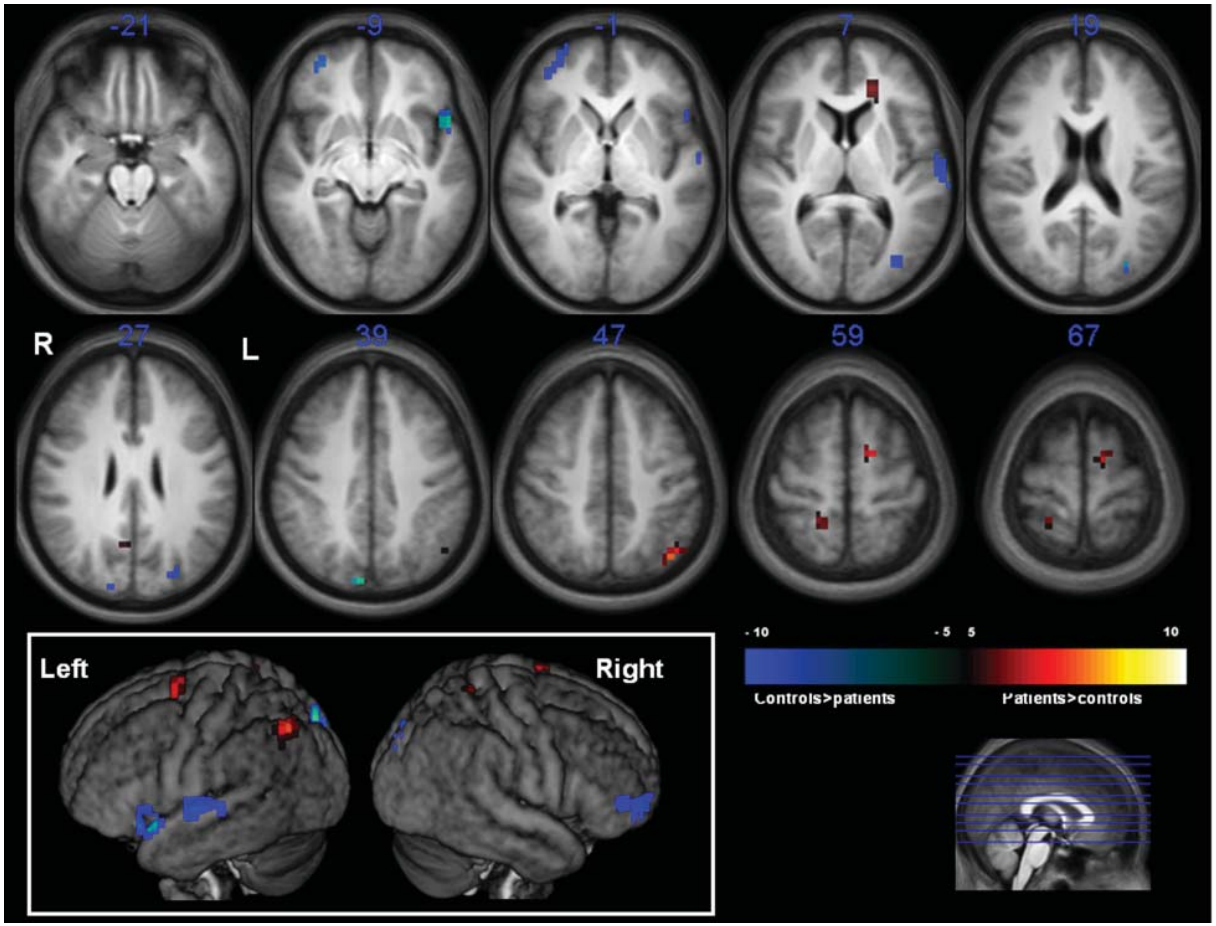

Figure 8.4 Group comparison of the pain-effect (painful *minus* non-painful stimuli) during stimulation of the CONTRA-ASYMPTOMATIC body region. Warm- and cold-coloured regions represent group differences in activity. Transverse slices, and 3D-rendering of surface of left and right hemisphere (box).

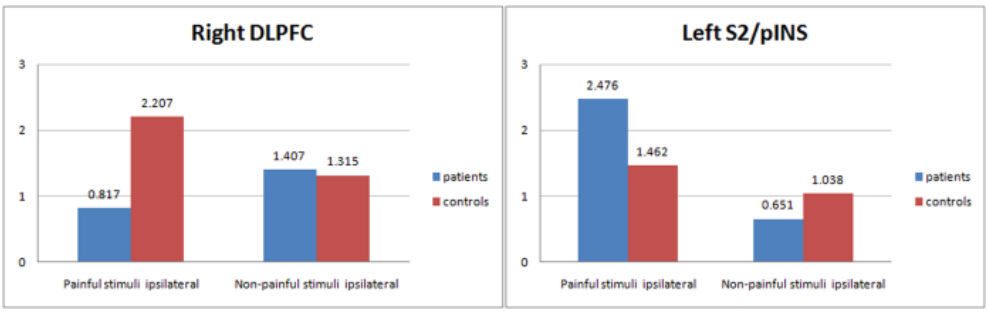

Figure 8.5 Contrast values per group in regions of interest, for painful and non-painful stimuli separately. DLPFC = dorsolateral prefrontal cortex; S2 = secondary somatosensory cortex.

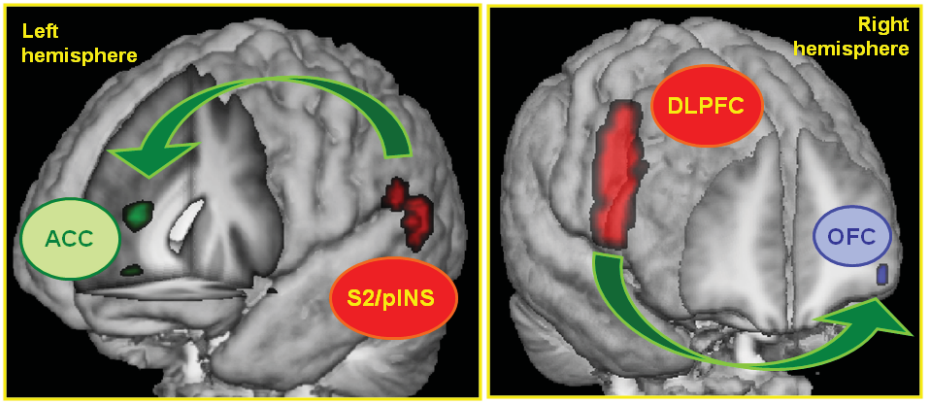

Figure 8.6 Schematic representation of results from psychophysiological interaction (PPI) analysis. This figure depicts group differences in changes in functional connectivity between a seed region and other brain regions in relation with the pain-effect (painful *minus* non-painful stimuli) in the IPSI-SYMPTOMATIC body region. (a) PPI analysis with left secondary somatosensory cortex/posterior insula (S2/pINS) as seed region; (b) PPI analysis with right dorsolateral prefrontal cortex (DLPFC) as seed region. ACC = anterior cingulate cortex; OFC = orbitofrontal cortex.

order to elicit painful stimulation and to avoid radiating sensations or motor responses. This stimulus method was effective in inducing similar perceived stimulus intensities for patients and controls but probably introduced increased variability in the measurement of pain thresholds. Many previous studies that were specifically designed to study the subjective pain experience in various CUP syndromes did demonstrate pain thresholds in CUP to be lower than in controls.[7]

The abnormal activation patterns we found occurred not only after painful stimulation of the symptomatic body region, but also of asymptomatic regions, which implies that augmented

cerebral pain processing in CUP is generalised in nature rather than restricted to a certain body region. The results of the current study, combined with our previous study that demonstrated – at the behavioural level – an inability of CUP patients to modulate (attenuate) pain perception during distraction, provide support for the notion of dysfunctional cerebral pain modulation, specifically involving prefrontal brain regions, as a key mechanism in the pathophysiology of functional pain syndromes.[20-22]

CUP patients showed high activity levels in sensory-discriminative regions of the pain matrix (S2/pINS), with low activity in regions involved in emotional-evaluative aspects of pain processing (such as DLPFC). In healthy subjects, distraction from pain is known to lead to a decrease in perceived pain intensity. This distraction-related attenuation of pain perception is mediated by activation of the descending pain modulatory system (DPMS), a system in which activity in specific brain regions, such as ACC, DLPFC, insula and amygdala, regulate the ascending pain signal at the brainstem level.[10] DLPFC is a key region in the DPMS, since its activity strongly modulates pathways between several (sub-)cortical regions during pain perception.[23] The role of DLPFC in higher-order (cognitive) pain modulation in CUP is further supported by the finding that variation of grey matter volume in DLPFC is associated with working memory performance in fibromyalgia.[24] The activation patterns we identified may well represent dysfunction of the DPMS.

From our data, it cannot be discerned whether the inability of the DPMS to exert top-down control over afferent nociceptive signals is a primary cause of CUP or rather the consequence of long-standing pathologically increased nociceptive input (secondary failure of the DPMS in response to continuous strong bottom-up pain signalling). However, both interpretations implicate an attenuated efficacy of DPMS as an important mechanism in CUP.

In PPI analysis, we found increased functional connectivity in CUP between operculo-insular cortex and ACC, and between prefrontal regions (DLPFC and OFC). ACC is involved in emotional-evaluative and attention-related pain processing,[9,25] and in attentional allocation to multiple sources of sensory input.[25,26] Also, ACC was found to inhibit operculo-insular cortex in normal pain processing.[27] Our finding of increased operculo-insular-ACC-connectivity may thus represent dysfunctional pain processing in the context of competing attentional sources. The increased connectivity between DLPFC and OFC further points towards dysfunction of DLPFC in exerting top-down control over pain processing. However, the exploratory nature of the PPI analysis is reason for caution in its interpretation.

Recent studies on chronic pain suggest abnormalities in cerebral network dynamics during rest, including disrupted connectivity in the 'default-mode network' (DMN) brain regions.[28-30] Our finding of increased activation in CUP patients in PCC, precuneus, lingual gyrus and several parietal brain regions (all DMN regions) during pain may be a consequence of disrupted resting-state network dynamics, which in turn lead to increased cerebral reactivity to external stimuli.

Certain limitations of our study have to be considered. First, our patient group included different pain syndromes and locations. This heterogeneity may contribute to variability in the imaging results, thereby reducing power for detecting differences. However, clinical and pathophysiological studies suggest that the distinction between the various CUP syndromes is arbitrary and thus irrelevant for the underlying neurophysiology.[2,3] Indeed, imaging studies on a variety of functional pain syndromes report abnormal cerebral pain processing, including prefrontal dysfunction.[21,22,31] Second, we cannot rule out that the use of analgesic medication influenced our results, although the influence of the medication used by our patients on attention and on cognition in general are probably limited.[32-34] Third, since this is a cross-sectional study, we cannot be fully certain whether the abnormalities in cerebral dysfunction are cause or consequence of chronic pain in CUP. Finally, electrical and other exogenous stimuli not equivalent to the spontaneous pain that patients experience, as has been demonstrated with neuroimaging in low back pain.[35] We used electrical stimuli because of their rapid onset and short stimulus times, which was essential in our rapid event-related design.

The potential of future functional neuroimaging studies in CUP does not only lie in providing an objective measure for visualizing abnormal pain processing; this method also offers the possibility to study the influence of several cognitive and psychological factors at the level of brain activity. As such, neuroimaging might prove to be more sensitive than behavioural outcome measures, potentially opening up new pathways for diagnosis and treatment. Further research should focus on (a) cerebral network dynamics in relation to evoked and spontaneous pain; (b) the comparison of medically explained and unexplained pain states, to explore whether our findings apply to chronic pain in general or whether they are specific to CUP; and (c) longitudinal studies of functional and structural changes in the brain in relation to acute into chronic pain.[36]

In conclusion, our present findings in patients with chronic, unexplained pain point towards inability of prefrontal brain regions to inhibit cerebral processing of painful stimuli, resulting in central amplification of pain.

ACKNOWLEDGEMENTS

The authors wish to thank S. de Jong, M.D., R. Kunze, M.D., and L.G. Exalto, M.D., for their help in subject screening; S.F. Neggers, PhD, for valuable comments on the design of the study; D.S. Veldhuijzen, PhD, for comments on a previous version of this manuscript; and B.B. Zandbelt, for advice on the connectivity analysis. This study was registered at Clinicaltrials.gov (NCT00463177).

REFERENCES

1. Snijders TJ, de Leeuw FE, Klumpers UMH, Kappelle LJ, van Gijn J. Prevalence and predictors of unexplained neurological symptoms in an academic neurology outpatient clinic - An observational study. J Neurol 2004;251:66-71.
2. Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? Lancet 1999;354:936-9.
3. Mayer EA, Bushnell MC. Functional pain disorders: time for a paradigm shift? In: Mayer EA, Bushnell MC, editors. Functional pain syndromes. 1st ed. Seattle: IASP Press; 2009. p. 531-65.
4. Smith GR, Jr., Monson RA, Ray DC. Patients with multiple unexplained symptoms. Their characteristics, functional health, and health care utilization. Arch Intern Med 1986;146:69-72.
5. McDermid AJ, Rollman GB, McCain GA. Generalized hypervigilance in fibromyalgia: evidence of perceptual amplification. Pain 1996;66:133-44.
6. Rollman GB, Lautenbacher S. Hypervigilance effects in fibromyalgia: pain experience and pain perception. In: Værøy H, Merskey H, editors. Progress in fibromyalgia and myofascial pain. 1st ed. Amsterdam: Elsevier; 1993. p. 283-309.
7. Snijders TJ, Ramsey NF, Koerselman F, van Gijn J. Attentional modulation fails to attenuate the subjective pain experience in chronic, unexplained pain. Eur J Pain 2010;14:282-10.
8. Hollins M, Harper D, Gallagher S, Owings EW, Lim PF, Miller V, et al. Perceived intensity and unpleasantness of cutaneous and auditory stimuli: an evaluation of the generalized hypervigilance hypothesis. Pain 2009;141:215-21.
9. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005;9:463-84.
10. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron 2007;55:377-91.
11. Koelega HS. Benzodiazepines and vigilance performance: a review. Psychopharmacology 1989;98:145-56.
12. Fruhstorfer H, Lindblom U, Schmidt WG. Method for quantitative estimation of thermal thresholds in patients. J Neurol Neurosurg Psychiatry 1976;39:1071-5.
13. Ramsey NF, Jansma JM, Jager G, Van Raalten T, Kahn RS. Neurophysiological factors in human information processing capacity. Brain 2004;127:517-25.
14. Burock MA, Buckner RL, Woldorff MG, Rosen BR, Dale AM. Randomized event-related experimental designs allow for extremely rapid presentation rates using functional MRI. NeuroReport 1998;9:3735-9.
15. Neggers SF, Hermans EJ, Ramsey NF. Enhanced sensitivity with fast three-dimensional blood-oxygen-level-dependent functional MRI: comparison of SENSE-PRESTO and 2D-EPI at 3 T. NMR Biomed 2008;21:663-76.
16. Worsley KJ, Liao CH, Aston J, Petre V, Duncan GH, Morales F, et al. A general statistical analysis for fMRI data. Neuroimage 2002;15:1-15.
17. Symonds LL, Gordon NS, Bixby JC, Mande MM. Right-Lateralized Pain Processing in the Human Cortex: An fMRI Study. J Neurophysiol 2006;95:3823-30.

18. Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. Psychophysiological and modulatory interactions in neuroimaging. Neuroimage 1997;6:218-29.

19. Brett M, Anton JL, Valabregue R, Poline JB. Region of interest analysis using an SPM toolbox [abstract]. Presented at the 8th International Conferance on Functional Mapping of the Human Brain, June 2-6, 2002, Sendai, Japan. NeuroImage 16, 497. 2002.

20. Desmeules JA, Cedraschi C, Rapiti E, Baumgartner E, Finckh A, Cohen P, et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. Arthritis Rheum 2003;48:1420-9.

21. Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, et al. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain 2004;127:835-43.

22. Stoeter P, Bauermann T, Nickel R, Corluka L, Gawehn J, Vucurevic G, et al. Cerebral activation in patients with somatoform pain disorder exposed to pain and stress: An fMRI study. Neuroimage 2007;36:418-30.

23. Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. Brain 2003;126:1079-91.

24. Luerding R, Weigand T, Bogdahn U, Schmidt-Wilcke T. Working memory performance is correlated with local brain morphology in the medial frontal and anterior cingulate cortex in fibromyalgia patients: structural correlates of pain-cognition interaction. Brain 2008;131:3222-31.

25. Peyron R, Garcia-Larrea L, Gregoire MC, Costes N, Convers P, Lavenne F, et al. Haemodynamic brain responses to acute pain in humans: sensory and attentional networks. Brain 1999;122 (Pt 9):1765-80.

26. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. Brain 1995;118:279-306.

27. Greenspan JD, Coghill RC, Gilron I, Sarlani E, Veldhuijzen DS, Lenz FA. Quantitative somatic sensory testing and functional imaging of the response to painful stimuli before and after cingulotomy for obsessive-compulsive disorder (OCD). Eur J Pain 2008;12:990-9.

28. Baliki MN, Geha PY, Apkarian AV, Chialvo DR. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. J Neurosci 2008;28:1398-403.

29. Cauda F, Sacco K, Duca S, Cocito D, D'Agata F, Geminiani GC, et al. Altered resting state in diabetic neuropathic pain. PLoS One 2009;4:e4542.

30. Napadow V, Lacount L, Park K, As-Sanie S, Clauw DJ, Harris RE. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. Arthritis Rheum 2010.

31. Kwan CL, Diamant NE, Pope G, Mikula K, Mikulis DJ, Davis KD. Abnormal forebrain activity in functional bowel disorder patients with chronic pain. Neurology 2005;65:1268-77.

32. Allen GJ, Hartl TL, Duffany S, Smith SF, VanHeest JL, Anderson JM, et al. Cognitive and motor function after administration of hydrocodone bitartrate plus ibuprofen, ibuprofen alone, or placebo in healthy subjects with exercise-induced muscle damage: a randomized, repeated-dose, placebo-controlled study. Psychopharmacology (Berl) 2003;166:228-33.

33. Lorenz J, Beck H, Bromm B. Cognitive performance, mood and experimental pain before and during morphine-induced analgesia in patients with chronic non-malignant pain. Pain 1997;73:369-75.

34. Rose EJ, Simonotto E, Spencer EP, Ebmeier KP. The effects of escitalopram on working memory and brain activity in healthy adults during performance of the n-back task. Psychopharmacology (Berl) 2006;185:339-47.

35. Baliki MN, Chialvo DR, Geha PY, Levy RM, Harden RN, Parrish TB, et al. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. J Neurosci 2006;26:12165-73.

36. Kupers R, Kehlet H. Brain imaging of clinical pain states: a critical review and strategies for future studies. Lancet Neurol 2006;5:1033-44.

SUPPLEMENTARY TABLES

Supplementary table 8.1 fMRI-results for pain-effect contrast (painful – non-painful electrical stimuli) from the ipsilateral, painful body region

Region	BA	Number of voxels	Peak Value	X	Y	Z
Controls						
Left S1	2/5/40	217	9.8	-40	-44	56
Right S1	2	34	7.8	20	-40	72
Left S2	13/40/42	193	10.3	-60	-20	12
Left M1	4/6	70	13.7	-16	-12	76
Left PMC	6	195	11.9	-12	-8	72
Right PMC	6	22	7.7	24	8	68
Left SMA	6	42	6.7	-4	4	72
Left SMA/mPFC	32	127	8.7	-4	12	44
Right SMA	6	20	8.7	12	-4	76
Right rACC	32	15	5.9	8	48	-4
Right SFG	8	20	7.7	28	32	56
Right SFG/MFG	10	63	9.5	24	60	28
Left DLPFC (MFG/IFG)	46	370	10.6	-48	44	12
Right DLPFC (MFG/IFG)	9	208	9.1	28	40	40
Right MFG	10	36	9.1	12	68	8
Left IFG, pars orbitalis	47	14	6.9	-20	28	-8
Right IFG, pars orbitalis	47	15	6.7	48	32	-4
Right OFC	10/11	40	8.0	16	52	-8
Left OFC	11	29	10.1	-24	52	-8
Left pINS	13	18	8.0	-44	0	-12
Right aINS	13	37	7.0	40	0	-16
Right pINS	21	33	6.1	36	-4	-8
Left STG (temporal pole)	22	93	10.0	-56	8	0
Left MTG	39	29	9.5	-60	-60	8
Right MTG	21/37	53	8.5	52	-20	-12
Left precuneus	7/31	205	11.2	-4	-60	64
Right precuneus	7	144	8.3	8	-64	44
Left SPG	7	151	9.6	-20	-64	56
Left caudate nucleus		113	7.8	-24	-20	20
Right IPG	40	45	7.6	36	-52	52
Right caudate nucleus		37	8.9	16	16	-12
Left Hippocampus		43	6.8	-16	-28	-4
Right thalamus		32	8.2	16	-12	-4
Left thalamus		55	7.9	0	-32	4
Right PCC	29/30	67	12.3	0	-44	12
Left calcarine sulcus	17/30	63	6.5	-20	-80	8
Left cerebellum	19	117	7.6	-20	-64	-20

Supplementary table 8.1 continues on next page

Supplementary table 8.1 *continued from previous page*

Region	BA	Number of voxels	Peak Value	X	Y	Z
Right cerebellum		91	7.8	24	-76	-20
Vermis cerebelli		32	7.7	4	-32	-16
Controls, deactivations						
Left cerebellum		11	-7.5	-4	-40	-52
Patients						
Right S1	1	23	7.3	20	-32	76
Left S1	3	150	11.1	-20	-36	68
Left S2/pINS/Rolandic operculum	13/22	460	11.9	-52	8	4
Right S2/pINS	13/21	108	7.5	40	-12	-8
Left M1	6	57	6.6	-16	-20	68
left PMC	6	79	8.3	-44	-4	48
Left SMA	6/24	39	10.0	-4	0	44
Left dACC	32	42	7.1	-4	16	36
left SFG	9	11	6.7	-16	52	40
Left DLPFC	9	79	7.3	-44	4	36
Left IFG	47	22	8.1	-48	36	0
Right IFG	22/47	132	9.5	56	12	4
Right aINS	45	10	6.5	32	32	8
Left STG (temp.pole)	38	22	7.8	-52	8	-12
Left MTG	22	115	9.3	-60	-52	12
Right MTG	13	40	6.4	44	-48	16
Left SMG	40	19	13.0	-52	-28	24
Right SMG	40	266	11.9	56	-28	28
Left precuneus	5/7	176	8.2	-16	-44	60
Left IPG	7	12	6.0	-36	-60	44
Right lingual gyrus	18	68	7.2	4	-84	-4
Left angular gyrus	39	24	6.7	-44	-60	24
Right hippocampus		10	6.4	20	-24	-8
Left caudate/lentiform nucl.		10	6.6	-24	16	0
Left thalamus		10	6.4	-16	-24	-4
Right cerebellum		194	9.7	20	-44	-48
Patients, deactivations						
Right DLPFC (MFG)	9	16	-6.4	28	20	40
Left MFG	10	12	-7.1	-36	60	4
Patients > Controls						
Right S2 / pINS/ TTG	13/40	14	-5.8	40	-28	8
Left S2 / Rolandic operculum	13/40	15	-5.6	-40	-24	24
Left SFG	9	20	-8.4	-12	52	40
Right lingual gyrus	19	35	-6.9	16	-56	-4
Left angular gyrus	39	11	-6.8	-44	-60	28

Region	BA	Number of voxels	Peak Value	X	Y	Z
Controls > Patients						
Right SFG	10	20	8.2	12	68	8
Right medial SFG	8	10	6.9	4	32	44
Right DLPFC (MFG)	8/9	230	7.8	28	40	48
Left DLPFC (MFG)	10/46	71	9.4	-48	40	20
Right IFG, pars triangularis	10	44	9.8	44	40	4
Right ITG	37	15	6.9	48	-48	-4
Left IPG	40	62	9.3	-40	-48	60
Left precuneus	7	18	7.8	0	-64	60
Right SPG	40	31	6.8	40	-48	56
Right PCC	29/30	34	8.6	0	-40	8
Right thalamus		13	6.6	16	-8	-4
Left cerebellum		42	8.0	-16	-76	-24

Activations for separate groups, and group comparison (patients *versus* controls). Coordinates are given in MNI space. aINS = anterior insula; BA = Brodmann Area; dACC = dorsal ACC; DLPFC = dorsolateral prefrontal cortex; IFG = inferior frontal gyrus; IOG = inferior occipital gyrus; IPG = inferior parietal gyrus; ITG = inferior temporal gyrus; M1 = primary motor cortex; MFG = medial frontal gyrus; MOG = medial occipital gyrus; MTG = medial temporal gyrus; OFC = orbitofrontal cortex; PCC = posterior cingulate cortex; pINS = posterior insula; mPFC = medial prefrontal cortex; PMC = premotor cortex; PT = planum temporale; rACC = anterior cingulate cortex, rostral part; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; SFG = superior frontal gyrus; SMA= supplementary motor area; SMG = supramarginal gyrus; SPG = superior parietal gyrus; STG = superior temporal gyrus; TTG = transverse temporal gyrus.

Supplementary table 8.2 fMRI-results for pain-effect contrast (painful – non-painful electrical stimuli) from the contralateral, asymptomatic body region. Activations for separate groups, and group comparison (patients versus controls). Coordinates are given in MNI space.

Region	BA	Number of voxels	Peak Value	X	Y	Z
Controls						
Left S1	2	11	7.7	-24	-40	72
Right S1	5	29	7.7	24	-44	72
Left S2/pINS/rolandic operculum	22/43	72	9.7	-60	0	4
Right S2/pINS	3/13/22	213	8.9	36	-12	12
Left M1	6	14	8.3	-20	-24	76
Right SMA	6	24	8.4	20	-4	76
Left PMC	6	19	6.9	-24	0	72
bilateral dACC	24/32	240	12.8	-4	16	36
Left PCC	30	39	7.2	-4	-52	16
Left mPFC	10	22	7.7	-4	68	16
Left SFG, medial	8	12	6.0	0	32	60
Left SFG	10	34	8.1	-28	68	12
Left IFG	46	12	5.8	-40	36	12
Left IFG	47	51	9.5	-44	20	-4
Left aINS	47	39	6.8	-32	20	-20
Left aINS	13	32	6.4	-36	12	4
Right aINS	47	16	8.0	28	12	-20
Left STG, temp pole	22	12	12.0	-52	16	-4
Right STG, temp pole	21/38	34	6.9	52	12	-16
Left MTG	39	18	6.5	-48	-60	20
Right MTG	22	12	6.1	52	-56	16
Left precuneus	31	37	6.6	-4	-64	28
Right precuneus	7	10	6.2	4	-56	64
Left lingual gyrus	17	10	6.3	-12	-88	-12
Right IOG	19	15	7.9	40	-80	-8
Left IOG	19	11	6.8	-32	-76	40
Right hippocampus	36	16	8.8	40	-20	-16
Right angular gyrus	39	11	6.6	56	-60	28
Left thalamus		38	6.1	-4	-8	16
Left caudate nucl		27	5.6	-4	0	16
Right caudate nucl		53	7.1	12	12	12
Right globus pallidus		16	6.7	8	4	-4
Left amygdala		12	6.1	-24	0	-12
Left hippocampus		15	7.4	-4	-12	-16
periaqueductal grey		104	9.6	12	-28	-8
Left cerebellum		164	11.0	-4	-52	0
Right cerebellum		85	7.0	20	-76	-20
Vermis cerebelli		19	5.6	4	-44	-20

Region	BA	Number of voxels	Peak Value	X	Y	Z
Controls, deactivations						
Left MFG	10	18	-6.9	32	56	24
Left IFG	45	13	-8.0	-60	32	4
Patients						
Left S1	2	56	9.8	-20	-40	72
Right S1	5	141	13.7	24	-44	68
Left S2/pINS	13	18	7.1	-44	-20	20
Right S2/pINS	2/13	268	10.5	44	0	-8
Left SMA	6	13	6.5	-16	0	68
Right SMA	6	20	6.4	16	-12	68
Left rACC	32	12	6.6	-20	36	8
Left dACC	24	154	11.1	-4	12	36
Right dACC	5	10	5.9	12	-32	52
Left PCC	30	76	7.1	-4	-48	20
Right PCC	31	34	8.2	4	-48	28
Right mPFC	10	19	6.5	4	60	12
Left mPFC	10	16	5.9	0	68	16
Left MFG	10/24	64	8.5	-28	52	28
Right IFG	47	14	9.0	56	16	0
Left aINS	13	67	10.3	-36	12	-16
Right aINS	47	11	7.0	36	20	-16
Left STG	22	16	10.6	-60	4	4
Right MTG	21/22	82	9.5	56	-44	4
Right ITG	37	17	9.1	44	-48	-24
Left putamen	34	32	7.0	-28	4	-12
Left precuneus	7	69	10.6	-8	-68	56
Right precuneus	7	59	9.6	4	-60	32
Left angular gyrus	7	49	11.7	-40	-68	48
Left SMG	40	108	10.5	-52	-28	24
Right SMG/angular gyrus	40	302	10.7	48	-28	24
Left IPG	40	54	7.3	-48	-48	56
Left hippocampus		10	6.3	-8	-12	-20
Right hippocampus		15	6.2	16	-24	-8
Right parahippocampal gyrus	47	10	7.7	20	8	-20
Left thalamus		12	5.7	-4	-20	16
Right caudate nucleus		19	6.8	0	8	4
periaqueductal grey		37	7.2	-8	-32	-4
Left cerebellum		387	8.8	-4	-72	-12
Right cerebellum		137	9.5	28	-40	-40

Supplementary table 8.2 continues on next page

Supplementary table 8.2 *continued from previous page*

Region	BA	Number of voxels	Peak Value	X	Y	Z
Patients, deactivations						
Left M1	6	12	-6.8	-56	-4	28
Right MFG	10	38	-11.2	36	52	-4
Left MOG	19	40	-8.7	-36	-80	12
Patients > Controls						
Left angular gyrus	40	18	-7.5	-44	-64	48
Left SMA	6	14	-7.0	-16	0	68
Right precuneus	7	14	-6.5	4	-56	36
Left rACC	32	11	-5.9	-20	36	8
Controls > Patients						
Right cuneus	19	15	10.2	8	-80	36
Left IFG	44/45	23	9.3	-52	16	-8
Left MOG	31	10	7.8	-28	-76	24
Right MFG/DLPFC	10	24	7.6	32	56	0
Left TTG	42	15	6.7	-64	-12	8
Right MTG	37	11	6.1	48	-72	0

For abbreviations: see supplementary table 8.1.

Supplementary table 8.3 Results from psychophysiological interaction (PPI) analysis, group comparison of changes in functional connectivity between seed regions and other brain regions during the pain-effect (painful – non-painful electrical stimuli) from the ipsilateral, painful body region. Coordinates are given in MNI space. For abbreviations: see supplementary table 8.1.

Region	BA	Number of voxels	Peak Value patients vs controls*	Peak Value controls	Peak Value patients	X	Y	Z
Seed region: right dorsolateral prefrontal cortex								
Patients > controls								
Left orbitofrontal gyrus	11	4	4.1	-2.9	4.7	-44	48	-8
Controls > Patients								
No significant activations								
Seed region: left operculo-insular cortex								
Controls > patients								
No significant activations								
Patients > controls								
Left ACC	9	3	3.7	-2.2	4.7	-12	44	20

* = positive values represent regions in which task-related connectivity values (t-values) are greater in patients than in controls

9

Summary and general discussion

CASE VIGNETTE: FOLLOW-UP

After history taking and physical examination, we concluded that Mrs. A. suffered from chronic, unexplained pain. The clinical findings were not consistent with a current neurological diagnosis such as nerve root compression or another defined medical condition.

As a first step, we discussed our findings with Mrs. A. We told her that her pain symptoms were real and that they were consistent with a chronic pain syndrome that was not directly related to a current underlying disease, but that should be considered as a disease in its own right. We explained how chronic pain may arise as a consequence of abnormal signals in the central nervous system that lead to increased sensitivity to sensations like touch and pain. We compared her pain to a car alarm that was too sensitive: a well-functioning car alarm only goes off if someone breaks into the car, but her car alarm can be released by any trigger, like when a cat jumps onto the car.[1] We started her on scheduled analgesics (paracetamol) for a limited period of time; a tricyclic antidepressant was considered, but the patient chose not to use this. Also, we discussed her daily activities, specifically physical exercise, and made a plan for gradual increase of her activities according to a time-contingent reactivation schedule, which means that she should try to stick to the planned activities at any given day; not more than planned on good days, not less on bad days.

At this first consult and a follow-up visit, Mrs. A. had many questions about our conclusion and plan, although she was happy that we 'took a serious look at her pain'. Her initial restraint gradually was replaced by enthusiasm when she was able to perform more daily activities, like meeting her friends and taking walks. Her pain very gradually decreased, although she reported she was never pain-free.

Over the next two years, she returned to the outpatient clinic a few times with exacerbations of pain and worrying, usually after a 'wrong movement'. Every time, we performed a physical examination to exclude new neurological abnormalities, which was negative each time. Repeating our explanation about her pain in combination with a short-term analgesic schedule led to quick amelioration of symptoms. Over the years, Mrs. A. became more able to manage exacerbations herself and she intensified her social life.

Chronic, unexplained pain (CUP) is characterized, by definition, by the absence of a well-defined cause. This absence and the many (pathophysiological and therapeutic) uncertainties surrounding CUP are common reasons why doctors find patients with CUP and other unexplained symptoms difficult to help.[2] However, the follow-up of the case of Mrs. A. illustrates that CUP may be a treatable condition that is best managed if the treating physician is aware of the biopsychosocial context of CUP and uses knowledge of this context in the communication with and treatment of the patient. With the research presented in this thesis, we aimed to expand this body of knowledge. In this chapter, we summarize our key findings, place these findings in the clinical and scientific context and provide clinical recommendations as well as suggestions for further research.

SUMMARY OF KEY FINDINGS

Part I: Epidemiology

In part I of this thesis, we studied epidemiological aspects of CUP, with special focus on its prevalence, reliability of the diagnostic label 'unexplained', determinants of pain severity and health-related quality of life (HRQOL) and prognostic factors.

In **chapter 2**, we prospectively studied all newly referred patients in a university outpatient clinic for Neurology. Of all new referrals, 35% presented with a somatic complaint that was eventually labeled as a medically unexplained symptom (MUS). Almost half of the patients with a MUS suffered from unexplained pain (15% of all new patients). The clinician's first impression (after reading the referral letter and first seeing the patient) and – to a lesser extent – a 'second opinion' referral type were good predictors in discriminating MUS from symptoms that could be attributed to a well-defined disease.

In **chapter 3-5**, we report results from the 'PROgnostic Factors In the Long-term Evaluation of chronic, unexplained PAIN' (PROFILE-PAIN)-study, a prospective two-center cohort study of 422 consecutively included CUP patients.

Chapter 3 discusses the reliability of labeling symptoms as 'unexplained'; previous studies in MUS in general (not specifically CUP) report varying rates of new diagnoses that provide an explanation for the original symptoms. We systematically evaluated the occurrence of such a new diagnosis for CUP during the 16-month follow-up-period both by patient self-report and by reviewing relevant medical charts. We found a low rate of misdiagnosis (1.6%) in CUP patients, which suggests that the uncertainty that surrounds the term 'unexplained' is usually unjustified.

We performed a cross-sectional analysis of the PROFILE-PAIN cohort (**chapter 4**) to identify determinants of pain severity and HRQOL in CUP. Psychological variables (somatization, catastrophizing and a dysfunctional coping style) turned out to be the strongest determinants

of pain severity and physical HRQOL. Sociodemographic variables barely contributed; only male gender and involvement in a pain-related medicolegal procedure were associated with poor physical HRQOL. Independent determinants for poor mental HRQOL were male gender and high degrees of anxiety and depression. Pain itself was an important determinant of physical, but not of mental HRQOL.

Chapter 5 focuses on the prognosis of pain and HRQOL in CUP. At 16-month follow-up of the PROFILE-PAIN cohort, 34% of patients experienced a clinically important decrease in pain severity. Patients who had higher baseline pain ratings were more likely to experience such a reduction of pain severity, although their pain was still more severe than in patients with low baseline pain. Apart from the baseline pain severity, none of the baseline (sociodemographic, pain-related and psychological) variables that we studied could reliably predict a decrease in pain severity during follow-up. For physical and mental HRQOL after 16-month follow-up some baseline variables did have predictive value, although the total explanatory power of these prognostic models was low. Male gender, high pain intensity and poor physical HRQOL were baseline predictors for poor physical HRQOL at follow-up. The only independent prognostic factors for poor mental HRQOL at follow-up were male gender and poor baseline mental HRQOL.

Although we studied a large number of factors that we selected from previous literature as possible determinants, the total amount of explained variance was limited, both in the cross-sectional and in the longitudinal study (**chapters 4 and 5**). This suggests that a large part of the variation in pain severity and HRQOL in CUP is determined by other factors.

In summary, CUP is a highly prevalent condition which we can diagnose reliably, but we know little about the factors that determine current and future clinical severity; established psychological and sociodemographic risk factors are of limited value.

Part II: Pathophysiology: pain sensitivity and cerebral pain processing

To study the intrinsic sensitivity for painful and non-painful somatosensory stimuli (the 'sensory profile') as a proxy for underlying pain mechanisms,[3] we used quantitative sensory testing (QST) in **chapter 6**. We compared QST findings of 85 CUP patients from the PROFILE-PAIN cohort with those of 89 healthy volunteers and found that CUP patients show increased sensitivity to painful heat, cold and pressure, but also decreased sensitivity for the detection of (non-painful) temperature stimuli, a profile that is not consistent with reported sensory profiles in other chronic pain states. QST findings were only moderately correlated to psychological characteristics, indicating that the sensory profile forms an independent factor in CUP etiology. Since pain hypersensitivity (as well as clinical symptoms) in CUP is thought to arise from central sensitization as a result of dysfunctional cerebral pain processing,[4] we studied the cerebral processing of pain and the effects of cognitive (attentional) modulation in CUP in chapter 7 and 8.

We studied attention-related modulation of the pain experience in a psychophysical study (**chapter 7**) in CUP patients with (mostly) unilateral limb pain and healthy control subjects. Subjects received painful and non-painful stimuli (individually thresholded). During the experiment their attention was either distracted from pain or focused towards pain. There was a tendency towards lower pain thresholds and higher VAS scores in CUP patients in all attentional states, but the groups differed most in their pain experience during distraction: whereas distraction from pain caused the expected attenuation of pain ratings in healthy controls, we did not find such an effect in CUP patients. This effect was pain-specific in that the effect of attention differed between groups for painful stimuli, but not for innocuous stimuli.

Chapter 8 describes the results of a functional MRI-study in which we further investigated our finding of decreased distraction-related pain reduction in CUP (from chapter 7) at the cerebral level, in matched groups of CUP patients and controls. We applied painful and non-painful stimuli (individually thresholded) during a cognitively demanding distraction task. The effect of pain was associated with well-known pain processing regions ('pain matrix') in healthy controls. In CUP patients, lower activity levels were found in dorsolateral prefrontal cortex and other prefrontal areas; in contrast, regions associated with sensory-discriminative aspects of pain processing, most notably operculo-insular cortex, were more active than in controls. Connectivity between operculo-insular and prefrontal cortex was increased in CUP patients during pain. These results suggest a (primary or secondary) dysfunction of in the prefrontal systems of descending pain modulation that usually cause inhibition of the pain experience during distraction.

The abnormalities in pain processing (effect of attention on pain scores, chapter 7), and pain-related brain activity (chapter 8) in CUP patients were spatially generalized: they occurred in the symptomatic *and* in the contralateral, asymptomatic limb. This spatially generalized pattern is further supported by preliminary analyses of our QST data that show that CUP patients with localized clinical pain (e.g. one arm) are equally hypersensitive in the symptomatic body region and in a contralateral, asymptomatic region.[5]

Overall, the studies in part II point towards a spatially generalized, pain-specific dysfunction of pain processing in the central nervous system (CNS) that leads to pain hypersensitivity.

DISCUSSION

CUP is a clinical reality. Results from our research show that CUP is highly prevalent, complex and multidimensional in nature, and that its outcome is unpredictable, though pain persists in most patients. Given this reality, the need for further research is self-evident.

The limits of epidemiology?

Epidemiological studies of CUP are hampered by the non-absolute case definitions in this heterogeneous clinical condition and the many – known and unknown – determinants at play. Our epidemiological findings in part I illustrate the complex interaction of sociodemographic and psychological factors in CUP. Since we studied a sample of patients whose pain was already chronic at baseline, the associations we studied represent a time frame beyond the phase of first transition from acute to chronic pain; in fact, in some cases of CUP, no acute phase can be identified at all. In this chronic stage, many (mostly psychological) factors are associated with pain severity and HRQOL in our cross-sectional analysis, but these same factors have little prognostic value for the development of pain and HRQOL over time. This limited prognostic value suggests that much of the variance in the clinical severity of CUP over time is either random or should be attributed to other factors. These other factors may include pathophysiological factors; further research into the pathophysiology of CUP has the potential to elucidate the mechanisms that connect risk factors with clinical pain, and increase our ability to predict clinical severity in CUP.

One practical implication from our epidemiological studies follows from the finding that pain severity and HRQOL in CUP are related, but are different in many aspects (e.g. in their relation with risk factors). This should be taken account in the design of therapeutic studies in CUP; ideally, such studies should incorporate both pain ratings and HRQOL as outcome measures. Recent recommendations from an international consensus group also propose that multiple (two or more) outcome domains should be evaluated in clinical trials for chronic pain.[6]

From pain hypersensitivity to dysfunctional cerebral pain modulation

In our QST study, we found pain hypersensitivity for several modalities in CUP. Recent psychophysical studies on different functional pain syndromes support the role of pain hypersensitivity and (central) sensitization in CUP.[7-9] The results of our pathophysiological studies on pain sensitivity, effects of attention and cerebral pain processing are convergent in showing that CUP is characterized by hypersensitivity to pain that: (a) is pain-specific, since sensitivity to innocuous stimuli is decreased rather than increased (see chapter 6); (b) is spatially generalized; and (c) responds abnormally to cognitive modulation such as distraction. This combination of findings points towards dysfunctional cerebral pain processing as a key mechanism in the pathophysiology of CUP. More specifically, a dysfunction of the descending pain modulatory system (DPMS) may well explain our findings, since this system is involved in top-down modulation of pain during cognitive modulations such as distraction from pain.[10] Many studies have shown that attention is an important factor in physiological pain processing,[11,12]

and psychophysical and neurophysiological data support a role of abnormal attention-related pain processing and hypervigilance in the pathophysiology of chronic pain.[13-16]

An increasing number of studies on underlying pathophysiological mechanisms in chronic pain, such as central sensitization, suggests that neurobiological mechanisms account for a substantial proportion of the (currently unexplained) variance in the severity and prognosis of clinical pain states.[4] This is supported by studies that report a predictive value of pre-operative QST measures in the occurrence of postoperative persistent pain.[17,18]

Some authors argue that CUP populations can be divided into a subgroup with aberrant pain physiology, which is expressed as pain hypersensitivity, and another subgroup with dysfunctional coping or primary psychological distress.[19,20] This dichotomy of CUP into 'CUP due to neurobiological dysfunction' and 'CUP due to psychological distress' carries the risk of replacing the age-old mind-body dualism ('psychological' *versus* 'organic' pain) with a new form of dualism: 'pain amplification-type' or 'psychological distress-type CUP'. This may lead to a scenario in which patients feel that they should be 'recognized' as 'pain amplification-type' CUP, if only to avoid the stigma of a 'psychological' condition. Perhaps more importantly, the empirical foundation for such a new dichotomy in CUP is limited. Although certain studies point towards two, more or less separate, subgroups,[19,20] other studies suggest that there is substantial interaction between psychological factors and pain amplification. Examples include studies in temporomandibular joint (TMJ) disorder: the finding that a widespread pattern of pain (which is related to pain hypersensitivity) is associated with high levels of somatization in TMJ,[21] and the fact that TMJ patients with high *versus* low degrees of hypersensitivity did not differ on psychological measures.[8] In our own QST study, we found some positive associations between measures of nociceptive and non-nociceptive processing (including paradoxical heat sensations, pressure pain and heat pain) and coping style (chapter 6). These latter findings support the non-dichotomous view that pain hypersensitivity and psychological distress are not mutually exclusive but instead interact and occur simultaneously within the same patient. Further studies should combine sociodemographic and psychological variables with measures of pain sensitivity (and possibly genetic risk factors) in the evaluation of CUP.[22,23]

The sensory phenotype as a proxy for pain mechanisms

Future studies on pain mechanisms and aberrant cerebral pain processing will profit greatly from the refinement of easily evaluable measurements of sensory signs and pain sensitivity, such as QST. Another example of a well-evaluable measure with relevance for underlying pain mechanisms is the study of the descending noxious inhibitory control (DNIC) effect, the phenomenon that the perceived intensity of a painful stimulus decreases in the presence of a second painful stimuli in a distant body site; this 'counterirritation' effect is closely related

to CNS mechanisms of descending pain modulation.[24] The closer a measurement (or group of measurements) is related to the underlying mechanism, the more likely it is that it will have prognostic and predictive value in therapeutic studies in CUP. Also, this measurement may serve as a proxy for the underlying mechanism in studies that dig deeper into the details of CNS mechanisms. Further refinement of psychophysical tests is needed to optimize the balance between mechanistic specificity and practical applicability.

Functional neuroimaging (functional MRI and other imaging techniques) has proven its value in the elucidation of CNS processing of experimental and clinical pain.[10,25,26] The future applications of functional neuroimaging in pain may be: (a) to further unravel the CNS mechanisms of CUP and chronic pain in general; (b) to study the precise relation of CNS mechanisms of pain processing with cognitive and emotional factors; and (c) to pinpoint the exact value of QST and other psychophysical techniques as markers of pain mechanisms. Apart from these pathophysiological applications, preliminary studies describe the potential of functional MRI as a therapeutic tool by providing chronic pain patients with real-time feedback of cerebral pain processing;[27] this intriguing development underscores the pivotal role of abnormal CNS processing in the pathophysiology of CUP.

CLINICAL IMPLICATIONS

On the basis of the study results that we described in this thesis, we venture to give the following recommendations for clinical practice:

1. If a physician concludes, after thorough clinical evaluation, that a patient suffers from CUP, the chances of finding a new diagnosis in the future that might retrospectively explain the pain are very small. Physicians can use this knowledge about the rarity of 'misdiagnoses' in their communication with the patient (chapter 3).
2. The current knowledge on risk factors and mechanisms in CUP offers insights that already are applicable in clinical practice. In general, a multi-axial work-up of a patient with chronic pain is important before determining the best treatment. Within this work-up, attention should focus on identification (or exclusion) of underlying diseases, on psychological and cognitive factors (including coping), on sociodemographic context and on previous therapy (chapters 4-5). The 'stepped care' model of therapy in CUP (chapter 1, box 1.1) may then be tailored according to the clinical profile of the individual patient.
3. QST-based sensory profiling (as a marker of underlying pain mechanisms) has a potential role in patient classification and in prediction of outcome and response

to treatment in CUP (chapter 6). However, the current lack of clinical validation studies on its exact diagnostic and prognostic value make that it is still too early to routinely implement QST-based sensory profiling of CUP in clinical practice.

4. In order to increase therapeutic options and success in CUP, medical schools and specialty training programs should (further) incorporate pain medicine and MUS into their regular curricula.

SUGGESTIONS FOR FURTHER RESEARCH

1. Clinical studies in CUP should use multiple outcome measures, including pain and (health-related) quality of life, since these outcome measures often do not behave in unison in CUP (chapter 4-5).

2. Studies that aim to identify the factors underlying pain severity, prognosis or effects of treatment in CUP should combine the measurement of sociodemographic and psychological measures with the evaluation of the sensory phenotype and with more direct measures of CNS processing of pain, such as functional neuroimaging (chapter 4-6 and 8). The following associations deserve special attention: (a) the relationship between clinical symptom severity, pain hypersensitivity, measures of (dysfunctional) descending pain inhibition (e.g. DNIC) and psychological factors; (b) the effect of attentional manipulation on hyposensitivity to non-painful temperature stimuli (which may form a compensation mechanism for pain hypervigilance in CUP).

3. QST and related tools should be further refined and validated for their use as a marker of underlying pain mechanism(s) and as a prognostic and predictive tool in the clinical management of CUP (chapter 6).

4. Researchers in the field of pain neuroimaging should control or measure the subject's attentional state during fMRI-scanning to avoid bias (chapter 7-8).

5. As soon as the clinical armamentarium and accompanying knowledge allow a mechanism-based classification of chronic pain, this should be followed by randomized clinical trials in CUP and other chronic pain states that compare the effects of mechanism-based treatment with the effects of conventional (disease- or symptom-based) treatment.

REFERENCES

1. van Wilgen CP, Keizer D. Het sensitisatiemodel: een methode om een patiënt uit te leggen wat chronische pijn is. Ned Tijdschr Geneeskd 2004;148:2535-8.
2. Carson AJ, Stone J, Warlow C, Sharpe M. Patients whom neurologists find difficult to help. J Neurol Neurosurg Psychiatry 2004;75:1776-8.
3. Jensen TS, Baron R. Translation of symptoms and signs into mechanisms in neuropathic pain. Pain 2003;102:1-8.
4. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011;152:S2-15.
5. Liem KS, Snijders TJ, van Gijn J, van Wijck AJ, Veldhuijzen DS. Quantitative assessment of sensory profiles in widespread versus regional manifestations of chronic, unexplained pain [poster presentation]. World Congress of Pain, Montreal 2010 August
6. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105-21.
7. Greenspan JD, Slade GD, Bair E, Dubner R, Fillingim RB, Ohrbach R, et al. Pain sensitivity risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case control study. J Pain 2011;12:T61-T74.
8. Pfau DB, Rolke R, Nickel R, Treede RD, Daublaender M. Somatosensory profiles in subgroups of patients with myogenic temporomandibular disorders and Fibromyalgia Syndrome. Pain 2009;147:72-83.
9. Nozu T, Kudaira M, Kitamori S, Uehara A. Repetitive rectal painful distention induces rectal hypersensitivity in patients with irritable bowel syndrome. J Gastroenterol 2006;41:217-22.
10. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron 2007;55:377-91.
11. Peyron R, Garcia-Larrea L, Gregoire MC, Costes N, Convers P, Lavenne F, et al. Haemodynamic brain responses to acute pain in humans: sensory and attentional networks. Brain 1999;122 (Pt 9):1765-80.
12. Tracey I, Ploghaus A, Gati JS, Clare S, Smith S, Menon RS, et al. Imaging attentional modulation of pain in the periaqueductal gray in humans. J Neurosci 2002;22:2748-52.
13. Veldhuijzen DS, Kenemans JL, van Wijck AJ, Olivier B, Kalkman CJ, Volkerts ER. Processing capacity in chronic pain patients: a visual event-related potentials study. Pain 2006;121:60-8.
14. Peters ML, Vlaeyen JW, van Drunen C. Do fibromyalgia patients display hypervigilance for innocuous somatosensory stimuli? Application of a body scanning reaction time paradigm. Pain 2000;86:283-92.
15. Crombez G, Eccleston C, Van den Broeck A, Goubert L, Van Houdenhove B. Hypervigilance to pain in fibromyalgia: the mediating role of pain intensity and catastrophic thinking about pain. Clin J Pain 2004;20:98-102.
16. Hollins M, Harper D, Gallagher S, Owings EW, Lim PF, Miller V, et al. Perceived intensity and unpleasantness of cutaneous and auditory stimuli: an evaluation of the generalized hypervigilance hypothesis. Pain 2009;141:215-21.

17. Lautenbacher S, Huber C, Kunz M, Parthum A, Weber PG, Griessinger N, et al. Hypervigilance as predictor of postoperative acute pain: its predictive potency compared with experimental pain sensitivity, cortisol reactivity, and affective state. Clin J Pain 2009;25:92-100.

18. Brandsborg B, Dueholm M, Kehlet H, Jensen TS, Nikolajsen L. Mechanosensitivity before and after hysterectomy: a prospective study on the prediction of acute and chronic postoperative pain. Br J Anaesth 2011;107:940-7.

19. Giesecke T, Williams DA, Harris RE, Cupps TR, Tian X, Tian TX, et al. Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors. Arthritis Rheum 2003;48:2916-22.

20. Arendt-Nielsen L, Henriksson KG. Pathophysiological mechanisms in chronic musculoskeletal pain (fibromyalgia): the role of central and peripheral sensitization and pain disinhibition. Best Pract Res Clin Rheumatol 2007;21:465-80.

21. Wilson L, Dworkin SF, Whitney C, LeResche L. Somatization and pain dispersion in chronic temporomandibular disorder pain. Pain 1994;57:55-61.

22. Smith BH, Macfarlane GJ, Torrance N. Epidemiology of chronic pain, from the laboratory to the bus stop: time to add understanding of biological mechanisms to the study of risk factors in population-based research? Pain 2007;127:5-10.

23. Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W. Idiopathic pain disorders--pathways of vulnerability. Pain 2006;123:226-30.

24. Van Wijk G, Veldhuijzen DS. Perspective on diffuse noxious inhibitory controls as a model of endogenous pain modulation in clinical pain syndromes. J Pain 2010;11:408-19.

25. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005;9:463-84.

26. Apkarian AV, Hashmi JA, Baliki MN. Pain and the brain: specificity and plasticity of the brain in clinical chronic pain. Pain 2011;152:S49-S64.

27. Decharms RC, Maeda F, Glover GH, Ludlow D, Pauly JM, Soneji D, et al. Control over brain activation and pain learned by using real-time functional MRI. Proc Natl Acad Sci U S A 2005.

Nederlandse samenvatting (Summary in Dutch)

ACHTERGROND

Ongeveer 20% van de algemene bevolking heeft chronische pijn. Bij een aanzienlijk deel van alle gevallen kan er geen medische oorzaak aangetoond worden voor de pijn. Dergelijke chronische, onverklaarde pijn (COP) gaat vaak gepaard met belangrijke hinder in het dagelijks leven en met hoge kosten voor individu en maatschappij, als gevolg van ziekteverzuim en frequente bezoeken aan zorgverleners. COP is dan ook een veelvoorkomend probleem in alle lagen van de gezondheidszorg.

In de praktijk zijn er vele soorten COP: wijd verspreid door het lichaam of heel plaatselijk, continu of in aanvallen. Vaak maken artsen een onderscheid tussen de verschillende vormen van COP op basis van locatie en beschrijving van de klachten: wijd verspreide spierpijn wordt dan 'fibromyalgie' genoemd en onverklaarde buikpijn met klachten bij de ontlasting 'prikkelbaredarmsyndroom'. Deze syndromen worden als groep aangeduid als *functionele pijnsyndromen*. Hoewel het aparte aandoeningen lijken te zijn, blijkt er veel overlap te bestaan in aard van de klachten, kenmerken van de patiënten en onderliggende mechanismen (pathofysiologie). Er wordt daarom ook wel gedacht dat het onderscheid tussen deze syndromen kunstmatig is en dat alle functionele pijnsyndromen samen één spectrum van COP vormen.

De oorzaak van COP is – per definitie – onbekend, wat wil zeggen dat er geen concrete ziekte of aanwijsbaar letsel gevonden wordt bij medisch onderzoek. Desondanks is er wel kennis over de factoren die een rol spelen bij het ontstaan en de instandhouding van COP: een combinatie van neurobiologische factoren (bijvoorbeeld bijkomende lichamelijke ziektes), psychische factoren zoals tekenen van angst en depressiviteit of een niet-productieve omgang met pijn (*coping*), en sociale factoren (bijvoorbeeld de gezins- en werksituatie) is van belang. Het *biopsychosociale* verklaringsmodel van chronische pijn, in het bijzonder COP, benadrukt dat er bij iedere patiënt een combinatie van deze factoren speelt en dat deze factoren elkaar onderling beïnvloeden.

Er is nog veel onbekend over de exacte aard en het gewicht van de verschillende factoren die van invloed zijn op COP. Ook de onderliggende mechanismen waardoor de verschillende factoren tot pijn leiden zijn nog grotendeels onbekend. Pathofysiologisch onderzoek van de laatste jaren wijst erop dat COP gepaard gaat met een overgevoeligheid voor zintuiglijke prikkels, vooral pijnlijke stimuli. Deze overgevoeligheid lijkt samen te hangen met een abnormale verwerking van pijnsignalen in het centraal zenuwstelsel, een fenomeen dat wordt aangeduid met de term *centrale sensitisatie*.

De vele vragen en onduidelijkheden over de oorzaken en mechanismen van COP dragen er toe bij dat het moeilijk is om patiënten goed voor te lichten en vooral om ze effectief te behandelen. De vooruitzichten van deze patiënten ten aanzien van herstel van pijn en verbetering van de kwaliteit van leven zijn dan ook vaak ongunstig.

Dit proefschrift is gericht op het vergroten van de kennis over de klinische en pathofysiologische factoren die bijdragen aan ernst en beloop van COP. In deel 1 van dit proefschrift beschrijven wij een aantal epidemiologische onderzoeken naar COP. Deel 2 gaat dieper in op de pathofysiologie van COP, waarbij de nadruk ligt op gevoeligheid voor lichamelijke prikkels en op pijnverwerking in de hersenen.

DEEL I: EPIDEMIOLOGISCH ONDERZOEK

In hoofdstuk 2 van dit proefschrift onderzochten wij alle patiënten die voor een nieuwe klacht verwezen werden naar een polikliniek Neurologie. Van deze patiënten bleek 35% klachten te hebben waarvoor geen lichamelijke oorzaak gevonden werd; bijna de helft van deze patiënten (15% van het totaal) had onverklaarde pijn. De eerste indruk van de behandelend arts (na het lezen van de verwijsbrief en de eerste ontmoeting met de patiënt) was een goede voorspeller om al vroeg een medisch onverklaarde klacht te kunnen onderscheiden van een klacht met een duidelijke medische oorzaak. Het feit dat een patiënt verwezen werd voor een tweede opinie had ook een redelijke voorspellende waarde voor een uiteindelijke diagnose van onverklaarde pijn.

De hoofdstukken 3-5 gaan over een onderzoek naar prognostische factoren bij het beloop van COP op de lange termijn (het PROFILE-PAIN-onderzoek). Het betreft een prospectief onderzoek in twee ziekenhuizen, met een cohort van 422 COP-patiënten.

Hoofdstuk 3 gaat in op de betrouwbaarheid van de vaststelling dat pijn 'onverklaard' is; eerder onderzoek bij patiënten met medisch onverklaarde klachten in het algemeen – dus niet alleen pijn – laat zien dat er soms na korte of langere tijd bij patiënten een nieuwe diagnose gesteld wordt die achteraf gezien de oorspronkelijke klachten verklaart, maar deze eerdere onderzoeken lopen nogal uiteen wat betreft de frequenties van nieuwe diagnosen. Wij onderzochten bij de patiënten in het PROFILE-PAIN cohort systematisch na 16 maanden of er een nieuwe diagnose was vastgesteld, met behulp van vragen aan de patiënt zelf en door zo nodig de relevante medische dossiers na te trekken. Slechts bij 1.6% van de patiënten constateerden wij dat de aanvankelijke diagnose van onverklaarde pijn onjuist was en dat er een nieuwe, verklarende diagnose was vastgesteld. Dit suggereert dat de onzekerheid die veel artsen en patiënten voelen bij de constatering dat pijn 'onverklaard' is, meestal onterecht is.

In een dwarsdoorsnede-onderzoek van het PROFILE-PAIN cohort (hoofdstuk 4) onderzochten wij welke factoren geassocieerd zijn met de intensiteit van de ervaren pijn en met de kwaliteit van leven. Drie psychische factoren waren de sterkste determinanten van pijnintensiteit en van fysieke aspecten van kwaliteit van leven. Dit zijn de neiging tot somatiseren (het ervaren en van lichamelijke klachten die niet medisch verklaard kunnen worden en het zoeken van medische hulp hiervoor), de neiging tot catastroferen (een negatieve basishouding

tegenover pijn) en een ineffectieve omgang met pijn (*coping*-stijl). Sociodemografische factoren hadden weinig invloed; alleen het mannelijk geslacht en betrokkenheid bij een juridische procedure in relatie tot de pijn waren geassocieerd met lage fysieke kwaliteit van leven. Mannen en patiënten met een hoge mate van angst en depressie hadden een relatief slechte mentale kwaliteit van leven. Pijnintensiteit zelf was een sterke determinant van lichamelijke, maar niet van mentale kwaliteit van leven.

Hoofdstuk 5 is gericht op de prognose van pijnintensiteit en kwaliteit van leven bij COP in het PROFILE-PAIN cohort. Bij vervolg-meting, 16 maanden na de eerste meting, bleek 34% een klinisch relevante vermindering van pijnintensiteit te hebben doorgemaakt. Patiënten met een hogere pijnintensiteit bij de eerste meting hadden een verhoogde kans op een pijnverbetering, maar hun pijn was bij vervolg na 16 maanden nog steeds intenser dan bij patiënten met lage pijnintensiteit bij de eerste meting. Geen van de andere onderzochte factoren bij de eerste meting was geschikt om een verbetering van pijnintensiteit te voorspellen. Enkele factoren hadden wel een voorspellende waarde voor de kwaliteit van leven na 16 maanden, maar slechts in zeer beperkte mate. Deze factoren zijn: mannelijk geslacht en lage kwaliteit van leven bij eerste meting. Hoge pijnintensiteit bij de eerste meting was alleen met fysieke aspecten van kwaliteit van leven geassocieerd.

In de onderzoekingen die in hoofdstuk 4 en 5 worden beschreven viel op dat er met de onderzochte factoren maar een beperkt deel van de variatie in ernst en prognose van COP verklaard kon worden. Dit suggereert dat een groot deel van de variatie in ernst en beloop van COP samenhangt met andere factoren dan de factoren die door ons zijn bestudeerd.

Samengevat is COP een veel voorkomende en accurate diagnose. We weten nog weinig over de factoren die met huidige en toekomstige klinische ernst van COP samenhangen; de psychische en sociodemografische risicofactoren die uit eerder onderzoek voortkwamen, blijken slechts beperkte prognostische waarde te hebben.

DEEL II: PATHOFYSIOLOGIE: GEVOELIGHEID VOOR PIJN EN CEREBRALE PIJNVERWERKING

Wij onderzochten de gevoeligheid van COP-patiënt voor pijnlijke en niet-pijnlijke stimuli met behulp van kwantitatief sensorisch onderzoek (*Quantitative sensory testing*, QST) (hoofdstuk 6). Het *sensorisch profiel* dat uit dergelijke testen naar voren komt, kan een aanwijzing geven over de onderliggende pijnmechanismen. Wij vergeleken de QST-gegevens van 85 COP-patiënten uit het PROFILE-PAIN-cohort met QST-gegevens van 89 gezonde vrijwilligers. Hieruit bleek dat COP gepaard gaat met een verhoogde gevoeligheid voor pijnlijke hitte, koude en druk op een spier, maar ook met verminderde gevoeligheid voor de waarneming van niet-pijnlijke

temperatuursprikkels. Dit profiel komt niet overeen met profielen die bekend zijn van andere, verklaarde vormen van chronische pijn. De QST-bevindingen lieten slechts een beperkt verband zien met psychische kenmerken van patiënten; daaruit valt af te leiden dat het sensorisch profiel een eigen, onafhankelijke rol speelt bij de ontstaanswijze van COP.

De waargenomen overgevoeligheid voor pijn en de klinische klachten bij COP zijn mogelijk het gevolg van centrale sensitisatie en abnormale cerebrale pijnverwerking. Om deze hypothese te toetsen, onderzochten wij de effecten van cognitieve beïnvloeding (verandering van aandachtstoestand) op de gerapporteerde pijnervaring en op pijnverwerking in de hersenen (hoofdstuk 7 en 8).

Wij onderzochten de aandachtsafhankelijke modulatie van de subjectieve ervaring van pijn in een psychofysisch experiment (hoofdstuk 7) bij gezonde vrijwilligers en bij COP patiënten met éénzijdige pijn aan een arm of been. De deelnemers kregen pijnlijke en niet-pijnlijke prikkels toegediend, waarbij de sterkte van de prikkel was aangepast aan de individuele pijndrempel. Tijdens het experiment werd hun aandacht afgeleid van de prikkel of juist daarop gericht. Er was bij COP-patiënten een tendens in de richting van lagere pijndrempels en hogere scores voor ervaren pijn in alle aandachtstoestanden. De duidelijkste verschillen tussen patiënten en gezonde vrijwilligers waren zichtbaar tijdens afleiding van pijn: bij gezonde vrijwilligers veroorzaakte afleiding, zoals verwacht, een daling van de pijnscores, maar bij COP-patiënten niet. Dit verschil was pijn-specifiek: er bestond een verschil tussen beide groepen wat betreft het effect van afleiding tijdens pijnlijke stimulatie, maar niet tijdens niet-pijnlijke stimulatie.

Hoofdstuk 8 bevat de resultaten van een functioneel MRI-onderzoek, waarin wij de bevinding van afwezige onderdrukking van de pijnervaring door afleiding bij COP (uit hoofdstuk 7) bestudeerden op het niveau van hersenactiviteit. Een groep COP-patiënten en een groep gezonde vrijwilligers ondergingen pijnlijke en niet-pijnlijke prikkels (afgestemd op de individuele pijndrempel) tijdens een mentaal inspannende afleidingstaak. Bij gezonde vrijwilligers bleek het effect van pijn gepaard te gaan met hersenactiviteit in gebieden waarvan bekend is dat zij betrokken zijn bij pijnverwerking (de *pain matrix*). Bij COP-patiënten registreerden wij verminderde activiteit in de dorsolaterale prefrontale cortex en andere prefrontale hersengebieden; daarentegen was er bij hen verhoogde activiteit in gebieden die normaliter betrokken zijn bij sensorisch-discriminatieve aspecten van pijnverwerking (registratie van plaats en intensiteit van pijn), vooral de operculo-insulaire cortex. De effectieve verbindingen (connectiviteit) tussen operculo-insulaire cortex en prefrontale cortex tijdens pijn waren versterkt bij COP. Deze resultaten wijzen in de richting van een (primaire of secundaire) functiestoornis in de prefrontale hersennetwerken die gewoonlijk zorgen voor onderdrukking van de ervaren pijn tijdens afleiding.

De afwijkingen in pijnverwerking (hoofdstuk 7) en bijbehorende hersenactiviteit (hoofdstuk 8) bij COP waren niet beperkt tot één plaats: de afwijkingen bestonden zowel in

de pijnlijke (symptomatische) lichaamszijde als aan de andere (niet-pijnlijke) lichaamszijde. Dit gegeneraliseerde patroon wordt ook teruggevonden in nadere analyses van onze QST-gegevens, waaruit blijkt COP-patiënten met plaatselijke pijn (bijvoorbeeld in één arm) evenzeer overgevoelig zijn in hun symptomatische arm als in hun tegenoverliggende, asymptomatische arm.

De onderzoeken in deel II wijzen in combinatie op een gegeneraliseerde functiestoornis van pijnverwerking in het centrale zenuwstelsel, hetgeen leidt tot overgevoeligheid voor pijn.

CONCLUSIES

Chronische, onverklaarde pijn is een veel voorkomend probleem, met een onzekere kans op verbetering. Er is een duidelijke samenhang tussen verschillende (vooral psychische) klinische patiënt-kenmerken enerzijds en de ernst van pijn en de kwaliteit van leven anderzijds, maar deze kenmerken blijken niet erg geschikt om de prognose van patiënten te voorspellen. Mogelijk hangt de variatie in prognose niet zo zeer samen met de bekende klinische kenmerken, maar vooral met de onderliggende pathofysiologische mechanismen van chronische pijn: individuele verschillen in de manier waarop pijnlijke stimuli in het zenuwstelsel verwerkt en bewust ervaren worden.

Op pathofysiologisch gebied staat overgevoeligheid voor pijn – en niet voor niet-pijnlijke stimuli – centraal. Deze overgevoeligheid is gegeneraliseerd (onafhankelijk van lichaamsregio) en de reacties op cognitieve modulaties zoals afleiding verlopen abnormaal. Onze bevindingen wijzen op een verstoring van de pijnmodulerende (prefrontale) systemen in de hersenen. Uit onze bevindingen en ander onderzoek blijkt dat deze verstoorde cerebrale pijnverwerking niet los staat van de psychische en sociale factoren die bij COP van belang zijn; er lijkt juist een complex samenspel tussen deze niveaus te zijn. Toekomstig onderzoek moet dan ook gericht zijn op het samenspel tussen al deze factoren en niveaus: de psychische, sociale en demografische kenmerken van patiënten, de klinisch ervaren pijn, de gevoeligheid voor pijnlijke en niet-pijnlijke prikkels (sensorisch profiel) en de cerebrale pijnverwerking. Het sensorisch profiel kan hierin dienen als een goed meetbare 'tussenstap' tussen de ervaren pijn en onderliggende mechanismen. Een belangrijk doel van toekomstig onderzoek is het ontwikkelen van een classificatiesysteem voor COP dat gebaseerd is op onderliggende mechanismen (in plaats van arbitraire syndromen per lichaamsdeel). Een dergelijk classificatiesysteem kan de basis vormen voor pijnbehandeling op maat, en daarmee voor een effectievere behandeling.